release of ten as the dividing line between a positive and a negative result Also during the earlier part of our work, we started counting the pulse rate twenty-five minutes after the injection, but in a few cases the maximum release took place within that time, so a twenty-minute period was adopted This has proved to be quite satisfactory

In all, we have carried out 256 tests on sixty-three cases of typhoid or paratyphoid B infections, fifty-seven of them being on males and six on females The dosage of the drug has been either one-thirtieth or one-thirty-third grain of atropin sulphate hypodermically, most of the tests being made with one-thirtieth grain Fifty-six were cases of typhoid fever, the diagnosis being confirmed by blood culture, or by a Widal reaction in dilution above 1 in 40 Five of the remaining seven cases were infections due to *B paratyphosus* B, while the remaining

TABLE 1—Results of the Atropin Test in Seven Cases Showing the Variability in Time of Appearance of a Positive Widal Reaction

Case No	Sex	Day of Disease	Release	Widal (Mac.)	Blood Culture
25537	♂	6 10	87-100 = 13 82- 88 = 6	5th day of disease, negative for B typhosus	Positive for B typhosus
25625	♂	9 13	77- 98 = 21 82- 88 = 6	8th day of disease, positive (1 80) for B typhosus	Positive for B typhosus
25662	♀	10 16	111-132 = 21 115-120 = 5	10th day of disease, positive (1 160) for B typhosus	Positive for B typhosus
25515	♂	5 10	94-110 = 16 86- 86 = 0	4th day of disease, negative for B typhosus	Positive for B typhosus
25521	♂	18 22	81-104 = 23 79- 86 = 7	18th day of disease, positive for B typhosus	Positive for B typhosus
25128	♂	11 15	98-116 = 18 95-100 = 5	15th day of disease, negative for B typhosus	Positive for B typhosus
25700	♀	9 15	106-122 = 16 114-122 = 8	8th day of disease, positive for B typhosus (1 80)	Positive for B typhosus

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Thirty-five of our cases were admitted to the wards early enough so that the first test, if positive, would be of some value in determining the appearance of the reaction The average of these thirty-five cases indicated that the reaction appeared on the eleventh day of disease, with

TABLE 2—Data Concerning Eleven Cases which Failed to Give a Positive Reaction to the Atropin Test

Serial No	Case No	Sex	Age	Day of Disease	Release	Widal (Mac)	Blood Culture	Remarks
1	25310	♂	32	6	99-116=17	Negative for B typhosus (5th day of disease)	Negative for B typhosus (5th day of disease)	Only 1 test diagnosis doubtful
2	25296	♂	32	11 25 31 42	60- 73=13 48- 65=17 57-101=44 82-100=18	Negative for B typhosus (10th day of disease)	Positive for B typhosus (10th day of disease)	
3	25281	♂	28	28	108-124=16	Negative for B typhosus (28th day of disease)	Positive for B typhosus (28th day of disease)	Died 9 days later, only one test made
4	25445	♂	18	11 19 27 31 35 38 41	99-126=27 88-100=12 66- 84=18 77- 92=15 76- 90=14 77- 90=13 72- 90=18	Negative for B typhosus (9th day of disease)	Positive for B typhosus (9th day of disease)	
5	25209	♂	33	10	94-110=16	Positive (1-20) for B typhosus (9th day of disease)	Positive for B typhosus (9th day of disease)	Died 10 days later, one test
6	25395	♂	18	15 20	86-104=18 80- 94=14	Positive for B typhosus (15th day of disease)	Positive for B typhosus (15th day of disease)	Died 29th day of disease
7	25096	♂	25	16	105-120=15	Positive (1-80) for B typhosus (12th day of disease)	Negative	One test
8	24958	♂	30	29	82-114=32	Positive (1-80) for B typhosus (9th day of disease)	Negative	One test
9	25691	♂	23	15 22 27	70-100=30 75- 92=17 96-120=24	Positive (1-80) for B typhosus (18th day of disease)	Negative	
10	25119	♂	33	17	74- 88=14	Positive (1-80) for B typhosus (14th day of disease)	Negative	One test
11	25653	♂	27	21 24 38 42	84-112=28 91-112=21 93-112=19 86-112=26	Positive (1-160) for B typhosus (20th day of disease)	Negative	

extremes from the fourth to the twenty-second days It must be remembered that in twenty-eight of these cases the reaction was positive with the first test, so it undoubtedly appears at a slightly earlier date It has been of great interest to us to observe that in twelve of

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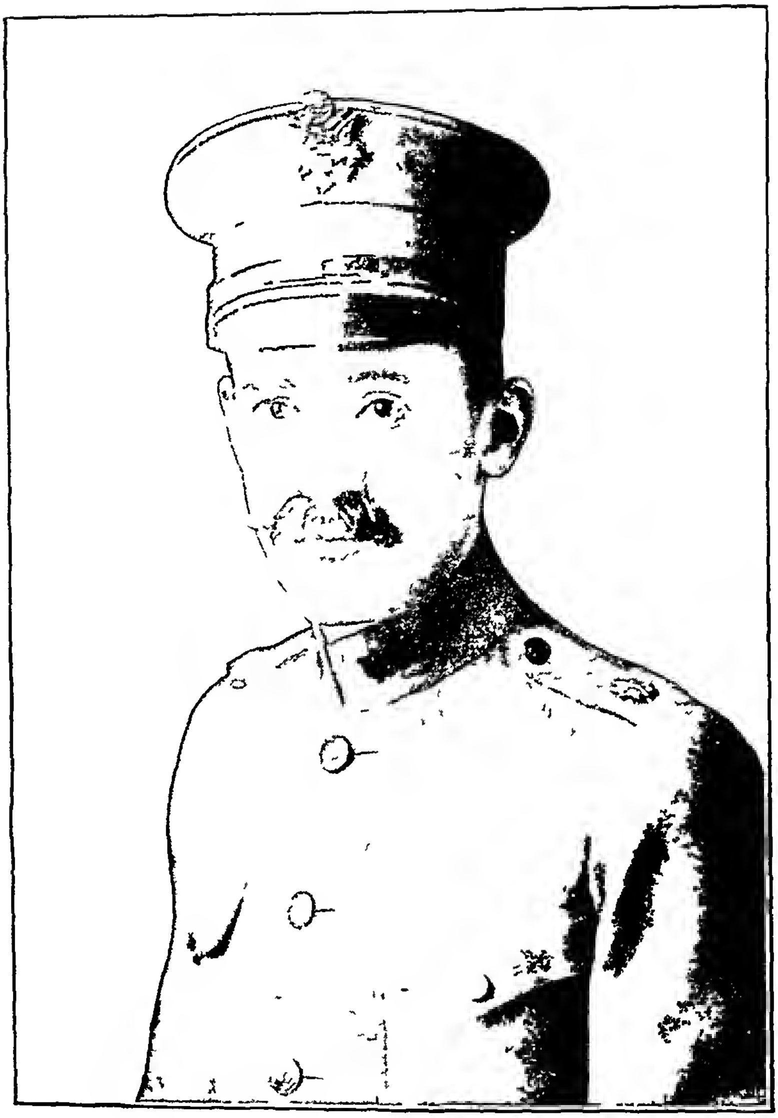
Theodore Caldwell Janeway, M.D.

1872-1917

Major, M.R.C., U.S. Army



THEODORE CALDWELL JANEWAY, M.D., a member of the editorial board of The Archives of Internal Medicine since 1908, died of pneumonia, Dec. 27, 1917, in Baltimore, aged 45 years. Dr. Janeway was born in New York City, Nov. 2, 1872, a son of Dr. Edward Gamaliel Janeway, the well-known diagnostician and consulting physician of New York, who died in 1911, and of Frances Strong Rogers Janeway. He married Miss Eleanor C. Alderson of Overbrook, Pa., Sept. 27, 1898, and is survived by his wife, two sons, Edward and Charles, and three daughters, Nora, Agnes and Francesca Janeway.

Dr. Janeway graduated from the Sheffield Scientific School of Yale University in 1892, and from the College of Physicians and Surgeons of Columbia University in 1895. He was instructor of bacteriology in Columbia University, 1895-1896, an intern in St. Luke's Hospital in 1897, instructor and lecturer in the University and Bellevue Medical College, 1898-1906, associate in clinical medicine in the College of Physicians and Surgeons of Columbia University, 1907, professor of medicine, 1909, visiting physician to St. Luke's, the City and the Presbyterian hospitals of New York City, physician-in-chief of Johns Hopkins Hospital and professor of medicine in the Johns Hopkins University under the Welch fund, 1914. He became secretary of the Russell Sage Institute of Pathology in 1907, and was a member of the Board of Scientific Directors of the Rockefeller Institute for Medical Research since 1911.

Dr. Janeway was a Fellow of the American Medical Association, a member of the Association of American Physicians, and of the Society of Experimental Biology and Medicine. His work in the different branches of clinical medical investigation, notably on the subjects of blood pressure and diseases of metabolism and the cardiovascular changes in nephritis, was especially noteworthy. He was the author of "The Clinical Study of Blood Pressure," published in 1904, and of many periodical articles.

Dr. Janeway offered his services to the Medical Department of the Army immediately after the declaration of war by the United States

and was assigned to active duty in the Surgeon-General's office at Washington with general direction of the Division of Internal Medicine The splendid personnel of the internists in charge of internal medicine and cardiovascular-renal diseases in the cantonments and camps was obtained largely through his efforts with the cooperation of Major Warfield T Longcope Just previous to his death, Dr Janeway had made a personal investigation of the outbreak of measles and pneumonia in some of the cantonments In addition to his continuous work in the Surgeon-General's office, he conducted two clinics a week in Baltimore, and it seems likely that this severe drain on his strength and energy weakened his power of resistance

Through his many scientific interests and connections, Dr Janeway did much to advance the growth of medical science in this country He was a man of lovable character, an energetic worker, and he gave himself wholeheartedly and freely to the many worth while undertakings to which he was called

The Archives of Internal Medicine

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THE VALUE OF THE ATROPIN TEST IN THE DIAGNOSIS OF TYPHOID FEVER*

EDWARD H MASON, M D
MONTREAL, QUE

With the recent publication of Marris'[1] article on the use of atropin in the diagnosis of the enteric group of infections, we decided to avail ourselves of the opportunity that the medical services of this hospital offered Therefore, within the last few months we have carried out the test according to Marris' technic on 109 patients, sixty-three of them suffering from typhoid, or paratyphoid B infections, and forty-six nontyphoid cases In all, 305 tests were performed The technic adopted is practically the same as that recommended by Marris, except that in most of our tests we have used one-thirtieth in place of one-thirty-third grain of atropin sulphate It is as follows

> On a fasting stomach the pulse rate is taken for ten consecutive minutes, while the patient rests quietly in bed If the rate per minute remains practically constant, this is accepted as the average mean rate Then one-thirtieth grain of atropin sulphate is injected hypodermically into the upper arm, after which the patient continues to remain quietly in the same position After twenty minutes have elapsed the pulse rate is taken again and the counting is continued until the maximum rate per minute has been reached and it has definitely started to fall to a lower level The difference between this high level and the mean of the ten consecutive minutes before the injection is taken as the release

In most normal persons the pulse rate increases from twenty to forty beats per minute after one-thirtieth grain of atropin sulphate hypodermically The increase is more marked in the earlier years of adult life, while after 50 it is not so great The question of sex seems to play no important part in regard to the degree of release Marris found this release to be so constant that he declared that an increase of only ten beats or less per minute was very suggestive that the patient was suffering from a typhoid or paratyphoid infection Releases between ten and twenty he considered to be doubtful, needing to be confirmed by further observations In our work we have taken a

* Submitted for publication July 24, 1917

* From the Medical Clinic of the Royal Victoria Hospital, Montreal

* I should like to acknowledge my appreciation of a grant from the James Cooper Fund of McGill University which made this work possible

1 Marris, F A Brit Med Jour, 1916, 2, 717

release of ten as the dividing line between a positive and a negative result Also during the earlier part of our work, we started counting the pulse rate twenty-five minutes after the injection, but in a few cases the maximum release took place within that time, so a twenty-minute period was adopted This has proved to be quite satisfactory

In all, we have carried out 256 tests on sixty-three cases of typhoid or paratyphoid B infections, fifty-seven of them being on males and six on females The dosage of the drug has been either one-thirtieth or one-thirty-third grain of atropin sulphate hypodermically, most of the tests being made with one-thirtieth grain Fifty-six were cases of typhoid fever, the diagnosis being confirmed by blood culture, or by a Widal reaction in dilution above 1 in 40 Five of the remaining seven cases were infections due to *B paratyphosus* B, while the remaining

TABLE 1—RESULTS OF THE ATROPIN TEST IN SEVEN CASES SHOWING THE VARIABILITY IN TIME OF APPEARANCE OF A POSITIVE WIDAL REACTION

Case No	Sex	Day of Test	Release	Widal (Mac)	Blood Culture
25537	♂	6 16	87-100 = 13 [illegible] = 6	5th day of disease, negative for B typhosus	Positive for B typhosus
25625	♂	9 15	77- 98 = 21 82- 88 = 6	8th day of disease, positive (1 80) for B typhosus	Positive for B typhosus
25662	♀	10 16	111-132 = 21 115-120 = 5	10th day of disease, positive (1-160) for B typhosus	Positive for B typhosus
25515	♂	[illegible] 10	94-110 = 16 86- 86 = 0	4th day of disease, negative for B typhosus	Positive for B typhosus
25521	♂	18 22	81-104 = 23 79- 86 = 7	18th day of disease, positive for B typhosus	Positive for B typhosus
25526	♂	11 15	98-116 = 18 95-100 = 5	15th day of disease, negative for B typhosus	Positive for B typhosus
25700	♀	9 15	106-122 = 16 114-122 = 8	8th day of disease, positive for B typhosus (1 80)	Positive for B typhosus

two ran a typical typhoid course, but at no time were we able to confirm our diagnosis by bacteriologic or by serologic methods Out of the sixty-three cases, eleven of them failed to give a positive reaction, that is a release of ten or less This is an exceedingly high percentage, but it may be partly accounted for by the fact that six of the eleven patients were given only one test Further, three of the eleven were extremely toxic and restless at the time of the test, which undoubtedly increased the release, all of these three patients dying a few days later

Only seven patients admitted showed a negative test before developing a positive one As this point determines the appearance of the reaction in relation to the day of disease the results are given in full (Table 1) From the seven cases recorded in Table 1 it would seem that the time of appearance of a positive reaction varies considerably

Thirty-five of our cases were admitted to the wards early enough so that the first test, if positive, would be of some value in determining the appearance of the reaction The average of these thirty-five cases indicated that the reaction appeared on the eleventh day of disease, with

TABLE 2—Data Concerning Eleven Cases which Failed to Give a Positive Reaction to the Atropin Test

Serial No	Case No	Sex	Age	Day of Disease	Release	Widal (Mac)	Blood Culture	Remarks
1	25310	♂	32	6	99–116=17	Negative for B typhosus (5th day of disease)	Negative for B typhosus (5th day of disease)	Only 1 test diagnosis doubtful
2	25296	♂	32	11 25 31 42	60– 73=13 48– 65=17 57–101=44 82–100=18	Negative for B typhosus (10th day of disease)	Positive for B typhosus (10th day of disease)	
3	25284	♂	28	28	108–124=16	Negative for B typhosus (28th day of disease)	Positive for B typhosus (28th day of disease)	Died 9 days later, only one test made
4	25445	♂	18	11 19 27 31 35 38 41	99–126=27 88–100=12 66– 84=18 77– 92=15 79– 90=11 77– 90=13 72– 90=18	Negative for B typhosus (9th day of disease)	Positive for B typhosus (9th day of disease)	
5	25209	♂	33	10	94–110=16	Positive (1–20) for B typhosus (9th day of disease)	Positive for B typhosus (9th day of disease)	Died 10 days later, one test
6	25595	♂	18	15 20	86–104=18 80– 94=14	Positive for B typhosus (15th day of disease)	Positive for B typhosus (15th day of disease)	Died 29th day of disease
7	25096	♂	25	16	105–120=15	Positive (1–80) for B typhosus (12th day of disease)	Negative	One test
8	24958	♂	30	29	82–114=32	Positive (1–80) for B typhosus (9th day of disease)	Negative	One test
9	25691	♂	23	15 22 27	70–100=30 75– 92=17 96–120=24	Positive (1–80) for B typhosus (18th day of disease)	Negative	
10	25119	♂	33	17	71– 88=14	Positive (1–80) for B typhosus (14th day of disease)	Negative	One test
11	25653	♂	27	21 24 38 42	84–112=28 91–112=21 93–112=19 86–112=26	Positive (1–160) for B typhosus (20th day of disease)	Negative	

extremes from the fourth to the twenty-second days It must be remembered that in twenty-eight of these cases the reaction was positive with the first test, so it undoubtedly appears at a slightly earlier date It has been of great interest to us to observe that in twelve of

these thirty-five cases the test was positive, with a negative Widal reaction and positive blood culture Also in four cases both Widal reaction and blood culture were negative with positive atropin tests, the former becoming positive at subsequent dates This would indicate that in a few cases the test might rival the blood culture as an early means of diagnosis

The disappearance of the reaction in relation to the day of disease and to the temperature is important In twenty-seven cases in which we were able to determine the former point the reaction averaged to disappear on the thirty-first day of disease The extremes ranged from the fifteenth to the fifty-fourth days As a rule, the temperature curve ranged between 98 to 100 F when the reaction disappeared, and in a few cases it reappeared slightly preceding a relapse with a rise in temperature

The eleven cases with their points of interest that failed to give a positive reaction (release of ten or less) during some period of their hospital stay are recorded in Table 2

We have had no experience with the use of the test in patients who have had typhoid vaccine Marris gave evidence to show that the test was positive within four weeks of such vaccination, which would make it of value only after that interval had expired

In order to control the work, forty-nine tests were carried out on forty-six ward patients suffering from a variety of clinical conditions Thirty-six of these patients were males, and ten were females The dosage in all cases except one was one-thirtieth or one-thirty-third grain and in that case it was one-seventy-fifth grain, as the patient was a boy of 13 years The releases varied from one to fifty-four, the average release for all cases being 21 5 beats per minute By sex the extremes are

Males (nonfebrile)	30 cases,	31 tests,	11 to 45
Males (febrile)	6 cases,	6 tests,	14 to 30
Females (nonfebrile)	7 cases,	9 tests,	1 to 54
Females (febrile)	3 cases,	3 tests,	13 to 50

Average release (all cases nontyphoid)	21 5
Average release males (nonfebrile)	23 6
Average release males (febrile)	18 8
Average release females (nonfebrile)	16 5
Average release females (febrile)	27 0

The foregoing figures show how variable the release may be in people who are not suffering from the enteric group infections Three females gave a release of ten or less, a positive reaction One, a case of acute bronchitis, on two occasions gave releases of one and eight, respectively The blood failed to agglutinate *B typhosus* or *B paratyphosus* A or B

The second case was one of tuberculous meningitis in a woman, aged 60, who also, on two occasions, gave releases of four and nine This may be explained by the well known hyperactive vagus which is present in certain cases of tuberculous meningitis

The third, a case of diabetes mellitus in a woman of 50, gave a release of ten In none of these three cases was there a previous history of typhoid fever or of typhoid vaccination

In the series of nontyphoid men there were four cases that each gave a release of eleven One was a patient who had vagotonia and who at the same time was taking 30 minims of tincture of belladonna per day He showed neither pupillary changes nor a dry mouth The other three were cases of gout, chronic arthritis, and multiple neuritis, respectively In all, pupillary changes were definite

Thus, when the five tests in the three females that released only ten or less are excluded, the total average release is 23 9, for males alone 22 8, and for females alone 32 8 This might indicate that females are more sensitive than males to one-thirtieth grain of atropin The types of cases covered in this group can be seen by the following diagnoses

AFEBRILE

Gout	Cerebral hemorrhage
Diabetes mellitus	Peripheral neuritis
Acute nephritis	Myalgia
Chronic diffuse nephritis	Vagotonia
Chronic arthritis, infectious	Cerebrospinal syphilis
Gonorrheal arthritis	Tabes dorsalis
Acute bronchitis	Splenomyelogenous leukemia
Chronic bronchitis	Chronic malaria
Pleurisy with effusion	Chronic appendicitis
Chronic pulmonary tuberculosis	Duodenal ulcer
Tuberculous meningitis	Cerebral concussion
Myocarditis	Sarcoma lumbar vertebrae
Thoracic aneurysm	

FEBRILE

Acute nephritis	Acute endocarditis
Acute bronchitis	Acute infectious arthritis
Pulmonary tuberculosis	Chronic infectious arthritis

On the nontyphoid group we have also worked out the minute that the high level of release first appears after the hypodermic injection of atropin We find it to vary from the fifteenth to the fifty-second minute The results are

Average of all cases	33 5 minute
Males (nonfebrile)	31 6 minute
Males (febrile)	34 0 minute
Females (nonfebrile)	28 7 minute
Females (febrile)	32 0 minute

The foregoing results would indicate that the release appears a little sooner in women than in men, and that in both sexes the non-

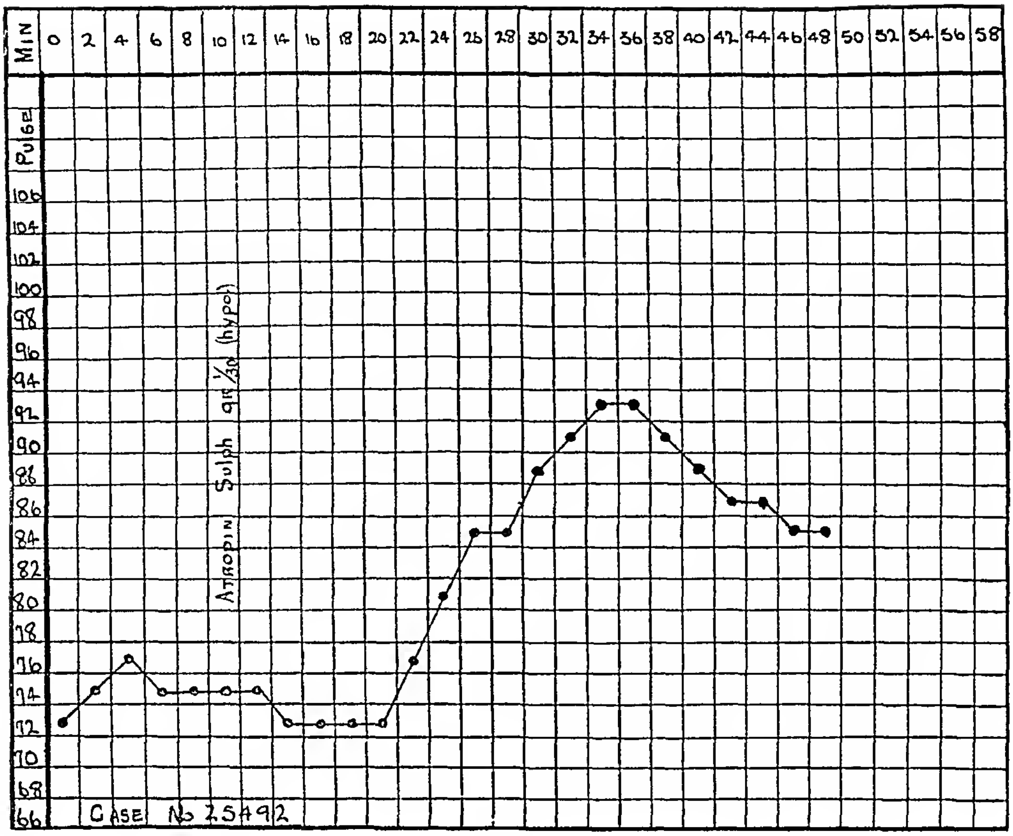

Chart 1

EXPLANATION OF CHARTS

The first three charts represent the complete pulse rate curve after the injection of one-thirtieth grain of atropin sulphate in three nontyphoid patients The scales explain themselves Chart 1 is taken in a case of diabetes mellitus and shows very clearly the release of 18 beats which took place, the high level of release being reached twenty-four minutes after the drug was given The slight slowing in rate which was maintained for 8 beats is of very common occurrence, due we believe to a hyperactive vagus before the partial paralysis takes place

Charts 2 and 3 show similar curves in cases of pleurisy with effusion and in pulmonary tuberculosis respectively, giving releases of thirty-two and thirty-one Note the slowed rate after the hypodermic for twelve beats in Chart 2

Charts 4 and 5 represent curves from cases of typhoid fever in the thirteenth and fourth days of disease The releases of two and of six make the reaction positive

Charts 6, 7 and 8, demonstrate the presence of the reaction throughout the course of three cases of typhoid fever, which diagnoses were confirmed by laboratory examinations The releases are represented in black and are read from the pulse scale at the extreme left The finest ruling represents two beats and the darker ones ten, the dividing line between a positive and a negative result The charts also show the relation between the reaction, temperature curve, and day of disease The facts of interest in each case are given under the charts

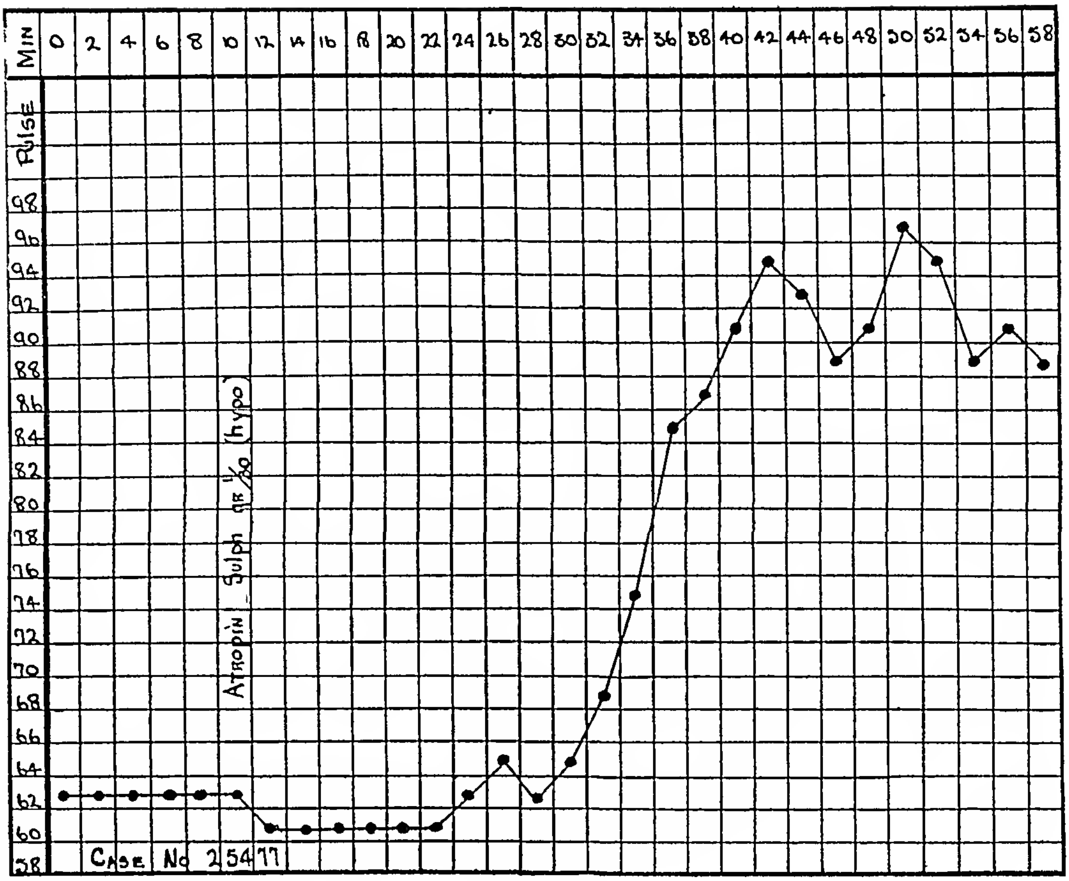

Chart 2

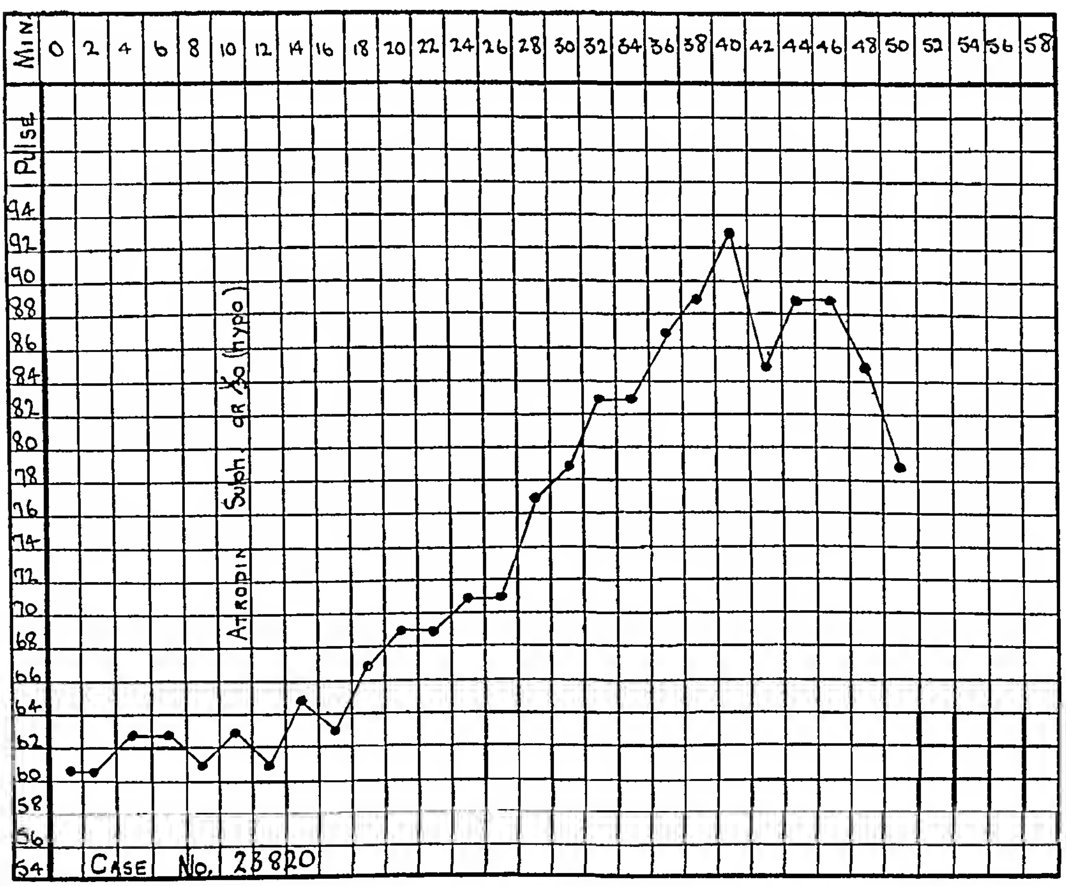

Chart 3

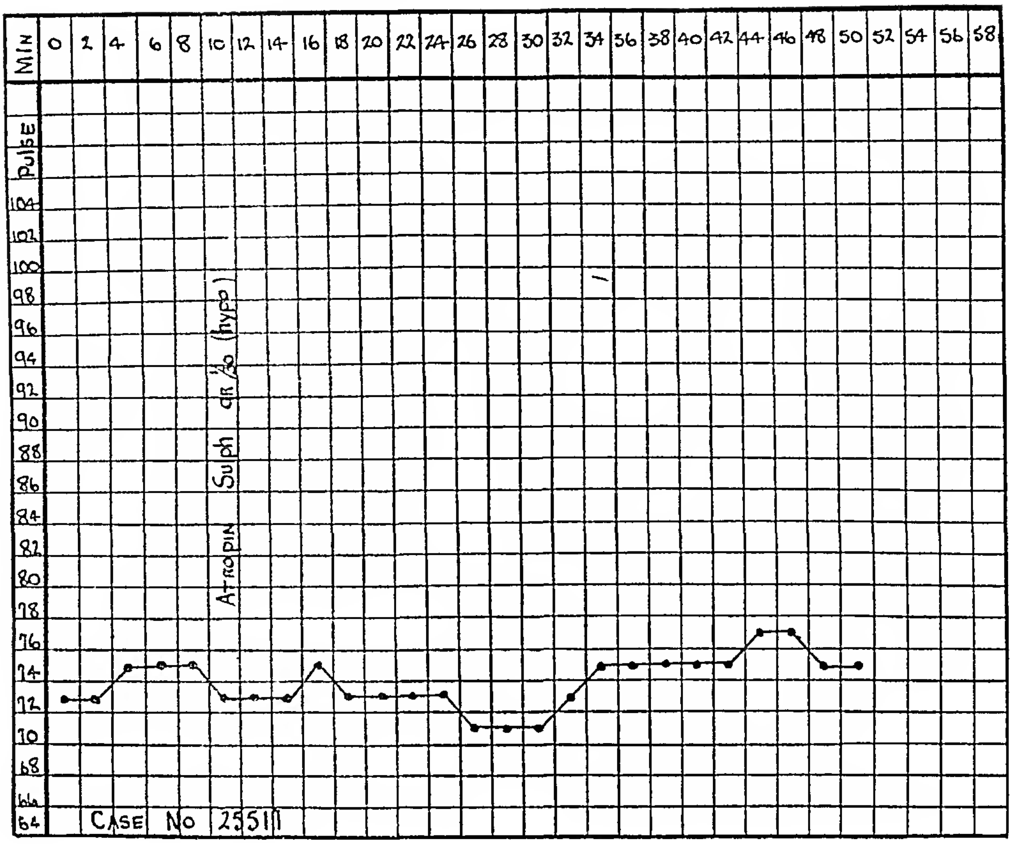

Chart 4

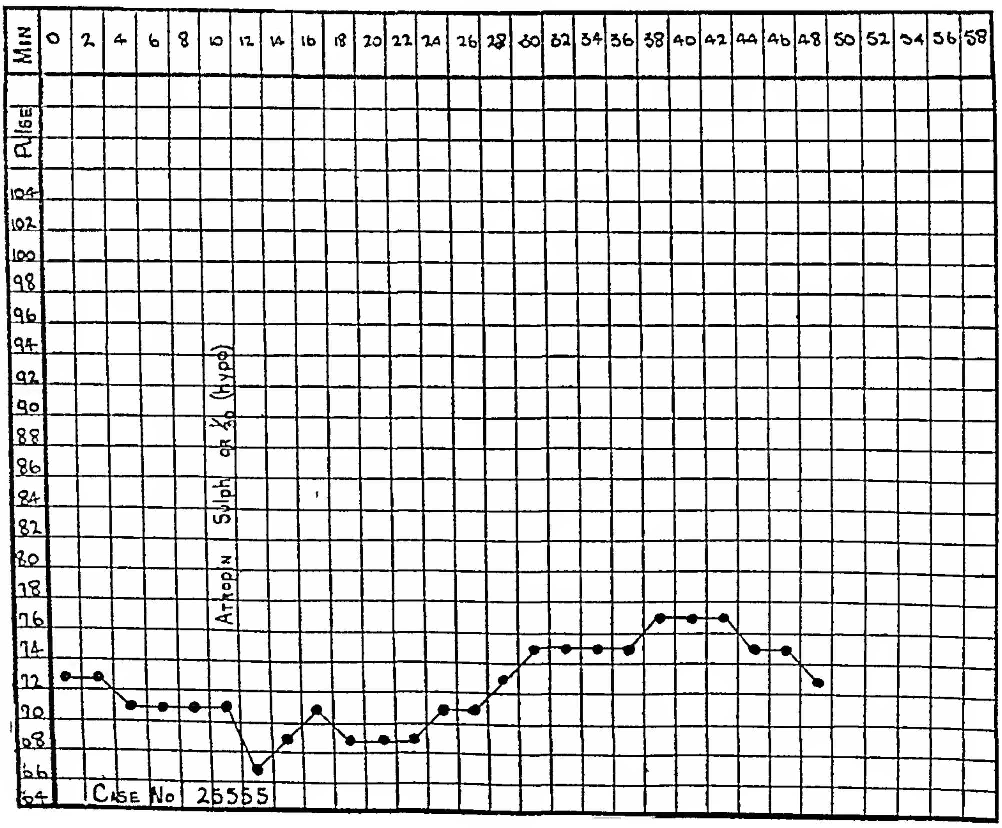

Chart 5

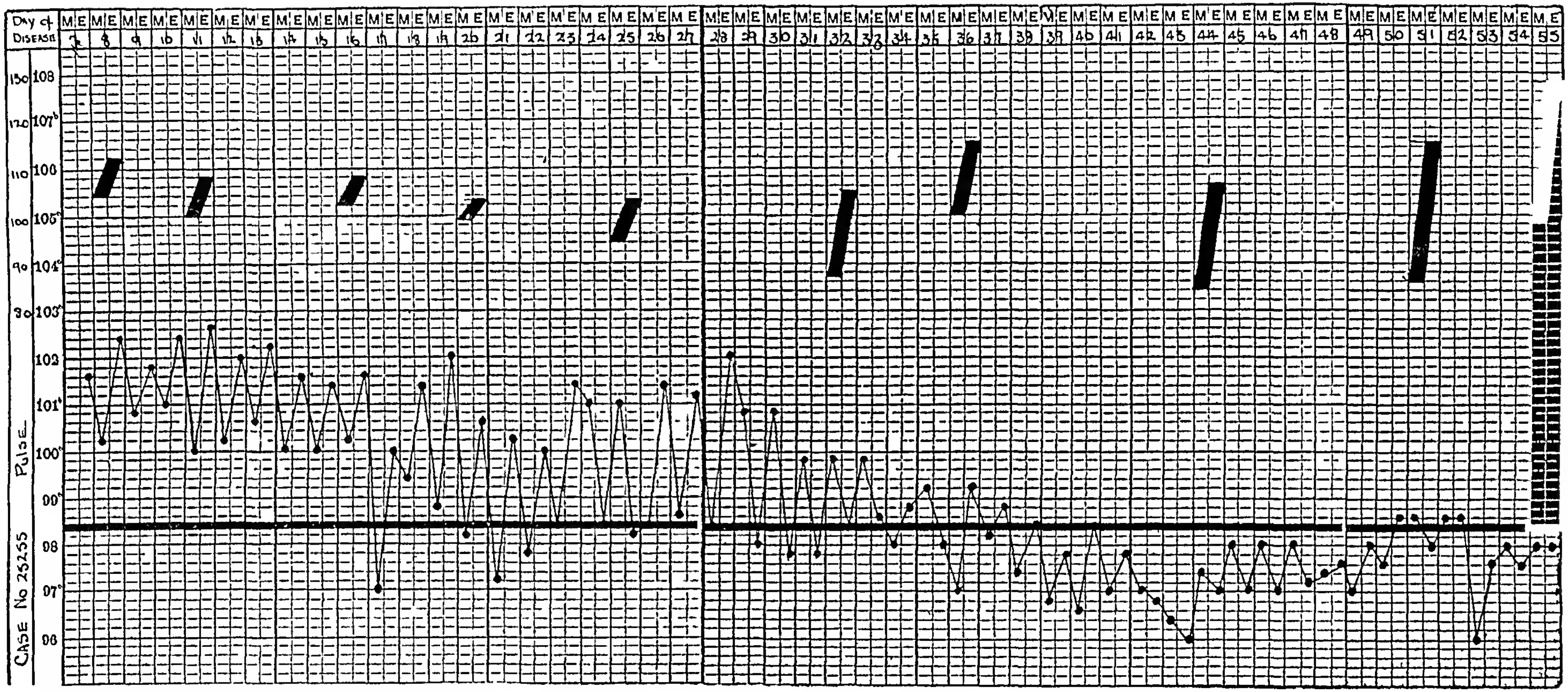

Chart 6—Man, aged 38, colored Diagnosis, typhoid fever, admitted on the seventh day of the disease, Widal reaction positive (1 680), blood culture positive Atropin tests Dose one-thirtieth grain atropin sulphate (hypodermically)

TABLE 3—TABULATED SUMMARY OF THE DATA RECORDED ON CHART 6

Number	Day of Disease	Release	Minute of Appearance of Maximum Release
1	8	102-111 = 9	33
2	11	100-108 = 8	35
3	16	102-108 = 6	39
4	20	99-103 = 4	24
5	25	92-103 = 11	38
6	32	87-105 = 18	36
7	36	100-115 = 15	33
8	44	82-106 = 24	31
9	51	86-115 = 29	25
10	55	98-128 = 30	25

TABLE 4—SUMMARIZED RECORD OF THE RESULTS ILLUSTRATED IN CHART 7

Number	Day of Disease	Release	Minute of Appearance of Maximum Release
1	8	92- 96 = 4	33
2	13	73- 76 = 3	30
3	16	83- 90 = 7	27
4	21	64- 76 = 12	29
5	25	57- 64 = 7	29
6	29	66- 78 = 12	35
7	32	65- 76 = 11	26
8	37	70- 80 = 10	24
9	44	77-106 = 29	22
10	48	65- 92 = 27	42

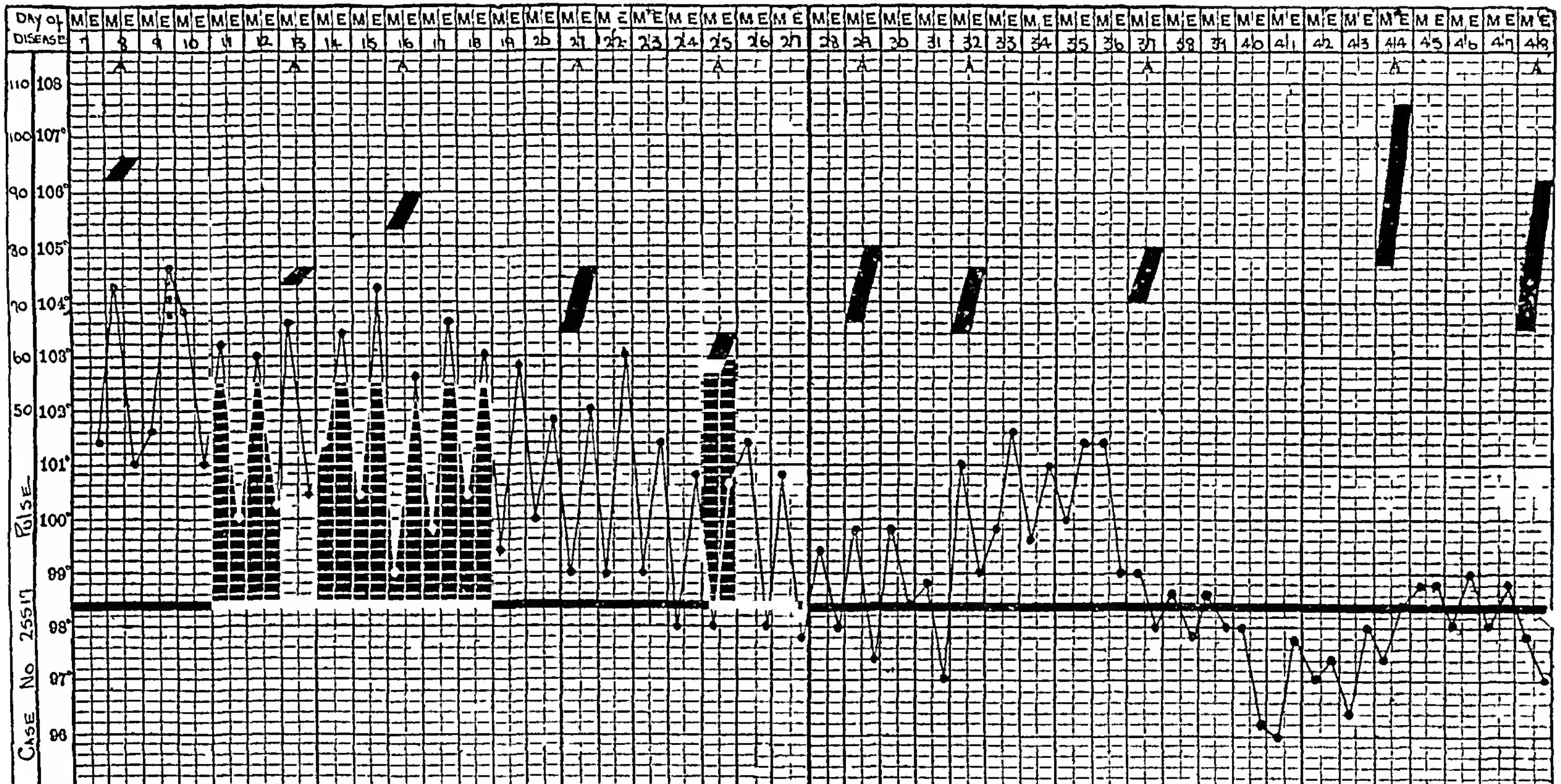

Chart 7—Male, aged 20, white Diagnosis, typhoid fever, admitted on the seventh day of the disease, Widal reaction negative, blood culture negative, Widal positive at a later date Atropin tests Dose one-thirtieth grain ofatropin sulphate (hypodermically)

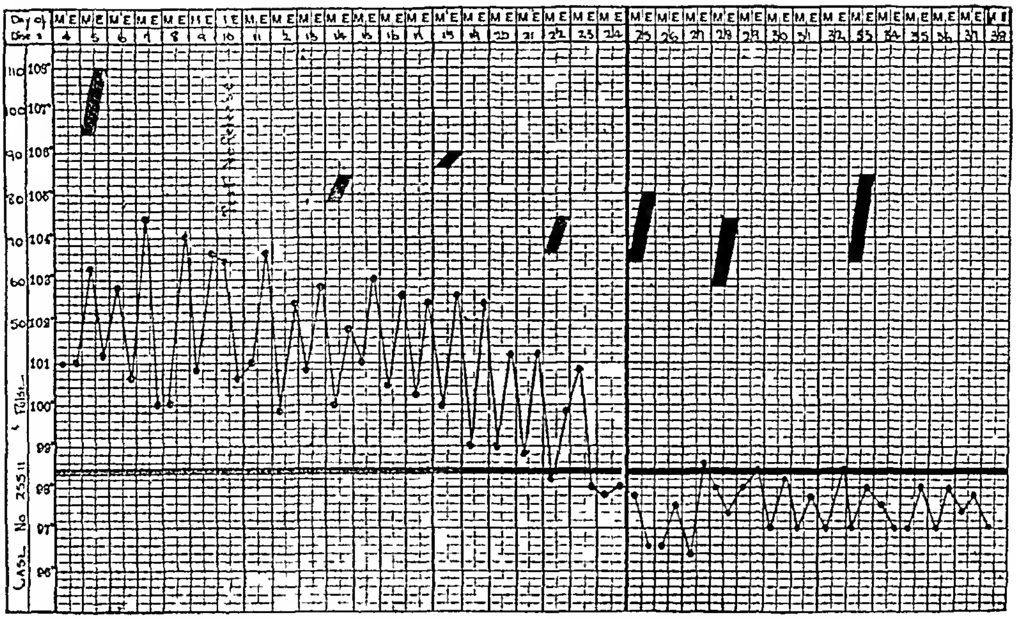

Chart 8—Man, aged 25 Diagnosis, typhoid fever, admitted on the fourth day of the disease, Widal reaction negative, blood culture positive Atropin tests Dose one-thirtieth grain atropin sulphate (hypodermically)

TABLE 5—Results of Atropin Tests Summarized from the Findings Recorded in Chart 8

Number	Day of Disease	Release	Minute of Appearance of Maximum Release
1	5	94-110 = 16	32
2	10	86- 86 = 0	0
3	14	78- 84 = 6	26
4	18	86- 90 = 4	36
5	22	66- 74 = 8	34
6	26	64- 80 = 16	32
7	29	58- 74 = 16	26
8	34	65- 84 = 19	31

febrile cases release more quickly than the febrile ones This early release was very evident with our women who had typhoid fever, and largely on that account did we adopt a twenty-minute interval instead of a twenty-five minute one before counting the pulse after the hypodermic injection

The subjective symptoms after one-thirtieth grain of atropin sulphate hypodermically in the patients having typhoid fever were almost nil, and in no case that gave a positive release did we find any pupillary changes In the nontyphoid group most of the patients had dilated pupils and dry mouths for a short time after the test Otherwise no bad effects were noted

SUMMARY

Three hundred and six atropin tests were performed on 109 patients, 63 typhoid patients or paratyphoid B patients, and 46 on nontyphoid patients Eleven of the typhoid group cases failed to give the reaction This has been discussed previously

The reaction becomes positive at about the tenth and disappears at about the thirty-first days of disease

In the nontyphoid group three cases gave a positive reaction We offer no explanation of these findings

In the diagnosis of fevers of the enteric group, we believe the test to be of great value, and in many cases undoubtedly precedes the Widal reaction

As a means of diagnosing the syndrome termed vagotonia we would suggest the use of atropin in the above manner

FACTORS IN RESISTANCE TO TUBERCULOSIS*

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When the literature dealing with the tuberculin reaction and immunity phenomena in general in relation to tuberculosis is surveyed it is rather surprising to note the decided skepticism which has found expression in recent times concerning the more or less current immunologic conception of the mechanism of the tuberculin reaction. Kraus, Landmann, Lowenstein and Volk, Aronson, Bessau, to mention only a few, have published observations which have led them to doubt the adequacy of the antigen-antibody conception. The fact that up to the present the major part of experimental work in tuberculosis has been along strictly immunologic lines, without apparently resulting in any substantial advance in our knowledge of the disease process or its therapy, is possibly the underlying reason that this skepticism has developed, for as yet no other adequate explanation has been put forward by the various workers which might serve as a basis for the diverging views. The existing confusion is due in part to the fact that immunologic ideas and terms have been maintained and used to express phenomena concerned with anaphylactic reactions as well as certain ferment changes; in part it is due to the fact that a large share of the literature is clinical in character and the observers have reiterated fallacious immunologic theories until the repetition has of itself seemingly carried the weight of uncontrovertible authority; perhaps, too, the fact that the effort is made to explain the skin reaction (von Pirquet) and the general reaction (subcutaneous) on one and the same basis, while as a matter of fact they are dissimilar in many important respects, has contributed in no small measure.

The whole trend of the study of tuberculosis has focused about the resistance to an established infection. The fundamental ideas concerning the factors involved in the establishment of the infection itself have been largely accepted, while the forces that protect the individual against infection are, from a practical standpoint, so largely social and economic that less interest has been attached to them from the experimental side. Until recent times, the idea that resistance to infection

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need not depend wholly on specific immune bodies has been largely ignored in experimental work, although the clinician was often compelled to rely solely on this uncertain factor in his treatment of the disease

The data presented in this paper represent observations along experimental lines not immunologic in the usual sense, but having to do rather with some of these nonspecific reactions on the part of the host If presented at all, it is with the hope that, however inadequate, they will be of interest in the interpretation of clinical problems as yet obscure

For the time being it may be well to keep in mind certain facts accepted by recent workers as fundamental to the discussion to follow These are the following (1) the cutaneous reaction appears to be specific and is related to a definite sensitization, the resistance to this reaction need not be specific, (2) the subcutaneous reaction has no relation whatever to antibody concentration of either serum or cells, when the disease focus (tubercle) is removed the reaction becomes negative, the reaction can be elicited by nonspecific methods, (3) tuberculin treatment has no specific significance and its beneficial effects have no relation to an active immunization The actual demonstration of an increase in antibody concentration in tuberculosis is not necessarily associated with favorable clinical results, recovery does not depend on the presence of specific antibodies

CASEATION

The tubercle bacillus differs from most other organisms in its abundant fat and wax content, some 35 to 45 per cent of the total dry weight consisting of lipoid bodies, including waxes, fatty acids and neutral fats When such bacteria undergo disintegration in the tissues this relatively resistant waxy material remains in situ for a considerable period of time It happens that these lipoids, being unsaturated, provided their state of dispersion be great enough, act as antiferments against tryptic and leukoproteolytic ferments This property of checking proteolysis depends, therefore, on both a chemical configuration — the number of unsaturated carbon bonds available, and on a physical basis — the ultimate state of division or dispersion These fat and wax bodies probably do not exist free as such either in the living bacilli or in the infected tissues after the death of the organisms, but most probably as an intimate protein-lipoid combination, that is, a combination in the physical rather than in the chemical sense

As the tubercle bacillus finds lodgment and multiplies in the tissues it entails the destruction of a certain number of tissue cells This is brought about through the excretion of toxic metabolic products, or

possibly through the medium of extracellular bacterial ferments Under ordinary pathologic conditions, tissue death is followed by autolysis and the removal of the fluid end-products through the vascular channels It is apparent that this does not take place in caseation, autolysis is in some way prevented and the necrotic debris accumulates It is true that the cellular reaction about the tubercle does not include polymorphonuclear leukocytes, which, because of their abundant proteolytic ferment content, liberated when they disintegrate, hasten autolytic processes, instead we find lymphocytes, the lipase carrying cells But tissue autolysis does not depend on the presence of polymorphonuclear leukocytes, and the absence of autolysis in caseous foci indicates some inhibitory factor The explanation for this is found in the presence of the unsaturated lipoids derived from the tubercle bacilli These are able to bind and inhibit the action of any autolytic ferments that may be present and thereby prevent autolysis That this is actually the case is readily demonstrated by the fact (*a*) that caseous material when extracted by the lipoid solvents will become digestible by trypsin, (*b*) that the lipoids extracted will act as antiferments and will, when injected into normal tissues, cause typical caseous foci Of equal importance is the fact that when caseous material is treated with iodin, which presumably saturates some of the unsaturated carbon bonds, tryptic digestion can take place

In general terms, we can consider the tubercle as a necrotic mass consisting of native proteins and of lipoids derived partly from the cells and partly from the tubercle bacilli, together with some of the higher and less diffusible protein split products Bounding this necrotic mass we have to consider connective tissue, endothelial cells, lymphocytes and a few polymorphonuclear leukocytes, the whole permeated with the tissue fluid, which in man contains only a moderate amount of lipase, some protease and peptidase, and a large amount of antiferment, the latter in an amount quite sufficient to overbalance any ordinary extracellular proteolytic activity The quiescent tubercle represents a balance between the digestive and digestion inhibitory forces, that is, it serves as a potential source of toxic split products derived from the necrotic material, potential rather than actual, because the active autolysis and removal into the circulation of the products of autolysis is prevented by the antiferment Any factor that will alter the conditions of this delicate balance so that autolysis can occur will bring about a toxic reaction, that is, a tuberculin reaction This may be brought about if we increase the ferments of the serum, or decrease the antiferment of the necrotic focus or of the serum It is apparent that such an alteration need have no relation to specificity

THE RELATIONS OF THE SERUM ALTERATIONS OF PREGNANCY AND MENSTRUATION ON THE TUBERCULOUS FOCUS

During the past few years we have become familiar with certain of the serum changes that take place during pregnancy With the aid of this knowledge we can follow the changes that occur in the tuberculous process as a result of these definitely understood serum alterations of pregnancy, in order to throw some light on the reactions involved

One of the first things that occurs after the onset of the pregnancy is a reduction of the blood and tissue lipases, the fat splitting ferments We have, as yet, no knowledge as to the source of these ferments, although there is evidence (Stuber) that points to glands of internal secretion as involved in the regulation of the production As a sequel of this lipase reduction an accumulation of fats and lipoids takes place in the blood stream This change in the blood lipoids is both quantitative and qualitative, as determined by numerous analyses[1] Inasmuch as the serum antiferment also consists of these lipoids, those that are unsaturated, we can expect an increase in the antiferment titer of the serum[2] This increase is so constant in pregnancy that the test for this antiferment rise has been repeatedly advocated as a test for pregnancy The increase comes on early, reaches the maximum at the time of labor and then rapidly — from five to seven days — returns to a normal level (Chart 1)

This antiferment rise is probably of decided physiologic importance in raising the threshold of protein metabolism In 1915, Jobling[3] showed that the rate of nitrogen excretion in the starving rabbit was almost inversely proportional to the level of the antiferment titer, that is, if the antiferment was high the rate of protein metabolism was low, if the antiferment was reduced, on the other hand, much nitrogen was excreted Wilson, in a paper published last year,[4] describes the metabolism of the pregnant woman in a way that leads one to believe that the relation that Jobling noticed in the rabbit holds good for the pregnant woman, and for a like reason, that is, the increase in antiferment brings about a positive nitrogen balance

In the particular case charted (Chart 1, after Wilson) a total storage of about 420 gm of nitrogen took place in the five-months' period of observation Even if the nitrogen of the birth products

1 Herrmann, E, and Neumann, J Wien klin Wchnschr, 1912, **25,** 1557 Frankel, S Wien med Wchnschr, 1913, **63,** 2198

2 Franz, R Arch f Gynak, 1914, **102,** 79 V Graff, E, and V Zubrzycki, J Ztschr f Geburtsh u Gynak, 1912, **72,** 303 Gammeltoft, S A Gynak Rundschau, 1913, **7,** 543

3 Jobling, J W, and Petersen, W F Ztschr f Immunitatsforsch, Orig, 1915, **24,** 219

4 Wilson, Karl Bull Johns Hopkins Hosp, 1916, **27,** 121

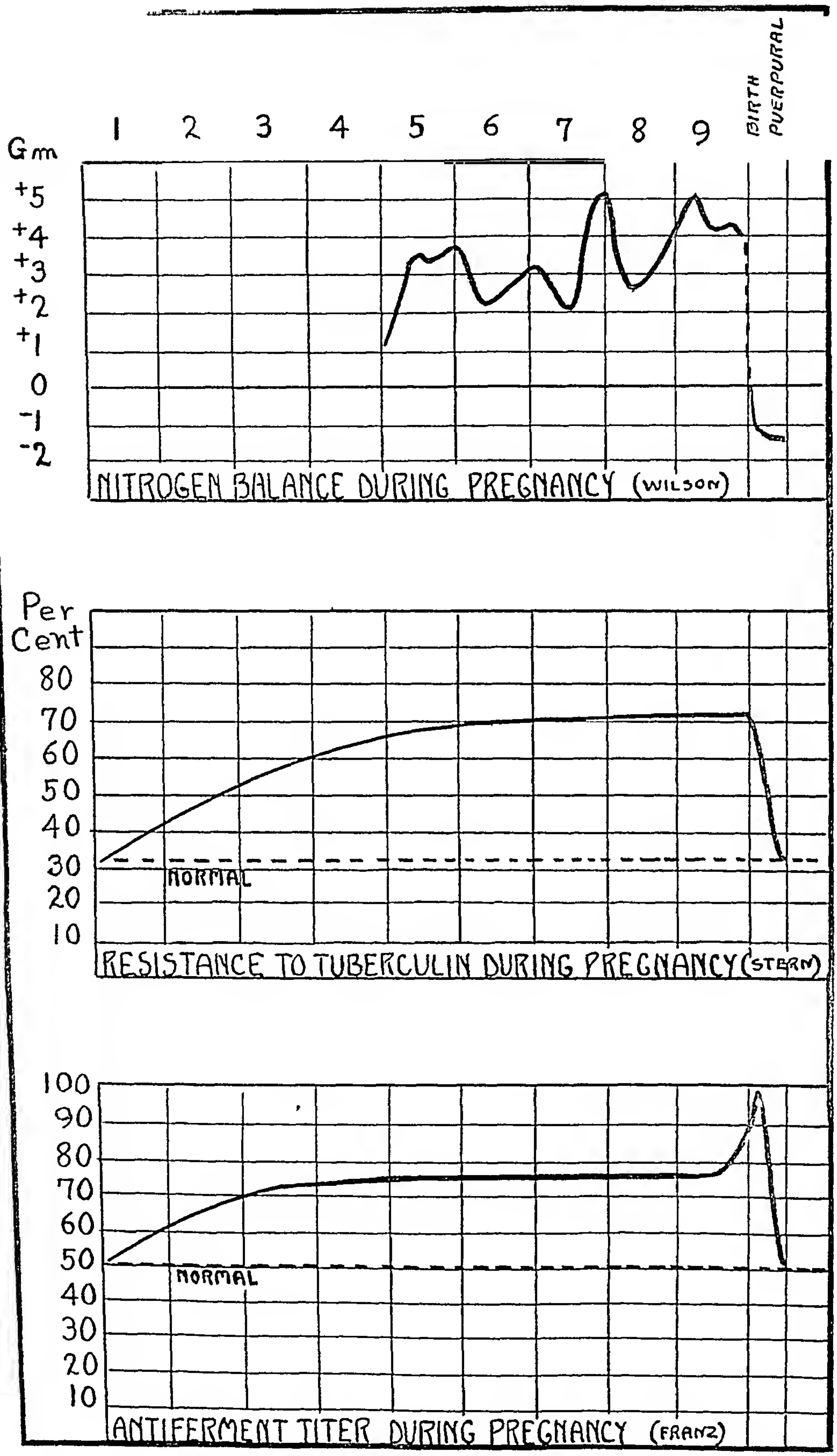

Chart 1—Relation of the antiferment during pregnancy to the nitrogen metabolism and resistance to tuberculin

and that estimated for the hyperplasia of the uterus and breasts is subtracted, Wilson considers that fully 285 gm of nitrogen were actually stored by the maternal organism in this case

Immediately after birth the nitrogen balance, as indicated in the chart, changes to the negative side, corresponding to the period in the metabolism when the antiferment titer rapidly falls, a time too, when the uterus must be digested back to its normal size

The sequence of events — lowering of the lipase activity, accumulation of lipoids in the serum, increase in the antiferment titer, checking of protein metabolism, the retention of nitrogen — seems simple and logical

Coincident with these changes, certain definite alterations occur in the titer of the proteolytic serum ferments (*a*) the ereptase or peptidase is increased to from two to four times the normal, throughout pregnancy, and remains at a constant level during delivery and the puerperal period, when uncomplicated, (*b*) the protease is increased to a small extent early in pregnancy and reaches a maximum immediately after delivery In the following table the average values for a series of pregnant women gives an idea of this relation (protease)

SERUM DIGESTION (CHLOROFORM METHOD AT 47 C, 24 HOURS)

Before delivery	0 03 mg per c c
1st day following	0 08 mg per c c
10th day following	0 00 mg per c c

This corresponds in general to the findings of the Abderhalden reaction, which is also augmented immediately after the delivery

Do these serum changes influence a coexisting tuberculous process? It is an accepted clinical observation that pregnancy, and particularly parturition, are decidedly detrimental to the tuberculous woman, the most pronounced activity developing as a rule immediately after delivery or shortly after the puerperium Even early in the pregnancy, cases which have been arrested are apt to give evidence, on careful examination, of focal activity while the general symptoms may remain suppressed

The reaction involving the balance that has been discussed as obtaining in the tubercle may be described somewhat as follows During the early stages of pregnancy the protease begins slowly to attack the fibrous connective tissue wall of the tubercle, small amounts of toxic material are liberated from the caseous focus, this in turn causing some local reaction on immediately adjacent tissues This effect of the protease is counterbalanced to some extent by the coincident increase in the antiferment, and also by virtue of the increase in the ereptase as a result of which the body is able to take care of a certain amount of toxic split products The net result of the altera-

tion of the ferment balance is a condition in which we may have a focal activation but also a more or less complete detoxication of the patient and feeling of well being This may continue until the time of delivery At this period two fundamental changes occur (1) the antiferment is diminished, and (2) a marked mobilization of protease takes place, both changes that favor proteolysis in the body The more resistant connective tissue is now rapidly digested, partly autolyzed toxic split products as well as bacteria are in consequence released and absorbed in some quantity, and the conditions are most

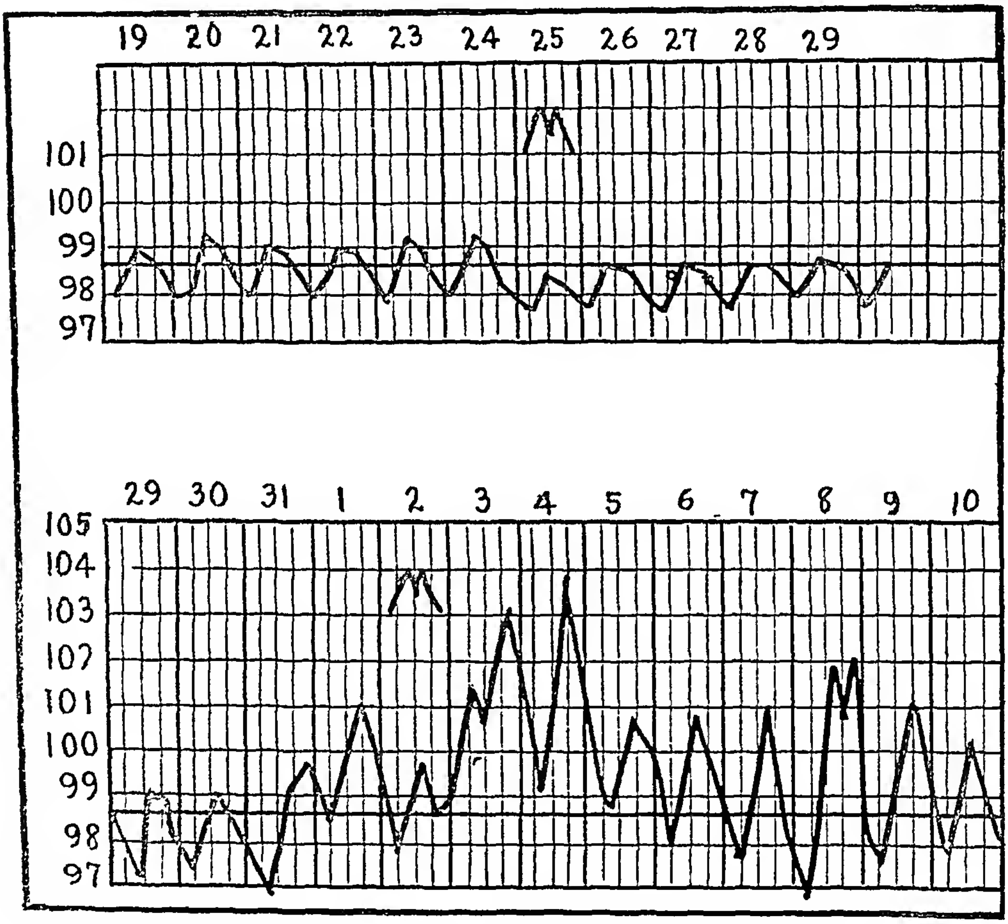

Chart 2—Effect of menstruation on the temperature curve of the tuberculous woman (after Pottenger) M—— day of menstruation

favorable for the rapid progress of the disease During this time the ereptase has not increased, and an accumulation of the toxic products may take place because their destruction is delayed In other words, the ferment-antiferment balance of the serum has been altered to such a degree that the local process is influenced unfavorably

This explanation along lines of ferment observation coincides exactly with clinical observation and the underlying facts have been established in a number of laboratories

We may now take another example, less complicated, because in it the antiferment changes do not take place to any extent and we have to deal solely with an increase in the proteolytic ferment It is known that the Abderhalden reaction becomes positive in every female for a period varying from three days to one week before menstruation, then promptly becomes negative again [5] The effect of the menstrual cycle on the temperature of the tuberculous woman is also a well known clinical phenomenon In incipient cases we usually find a slight increase in temperature just preceding menstruation, in advanced cases a stormy febrile reaction lasting a week or more may be ushered in The two charts (Chart 2) which are from Pottenger's book,[6] illustrate such cases Here again, the proteolytic ferments are evidently able to attack connective tissue, expose the necrotic foci and with the coincident hyperemia wash into the circulations some of the toxic split products that have accumulated

These two examples — pregnancy and the menstrual cycle — have been made use of here simply to make clear the one fact that we are dealing with conditions in which immunologic factors, as usually understood, are not concerned, so that these temperature reactions and activation of latent foci need bear no relation to antibody reactions, and we may dispense with them for the time being in the discussion of these special conditions

THE TUBERCULIN REACTION

When Koch introduced tuberculin in the therapy of tuberculosis he did so with the clear-cut idea of inducing an active immunization Under the method of administration as recommended by him, active immunization did occur That is, a demonstrable increase in antibodies — bacteriolysins, agglutinins and precipitins — was noted, but despite this augmentation patients frequently went to a fatal termination under circumstances that warranted the belief that the tuberculin treatment had harmed them

We have at present no clear-cut evidence that resistance to an established tuberculosis is related to antibody concentration of the serum or tissues Titze[7] as a result of extensive animal experiments says "nothing speaks with any certainty for the fact that the organism destroys the invading tubercle bacilli through the agency of antibodies

5 Baumann, E Monatschr f Geburtsh u Gynäk, 1915, **42,** 199 Van Waasbergen, G H Monatschr f Geburtsh u Gynak, 1915, **42,** 230 Kjaergaard, S Zentralbl f Gynak, 1914, **38,** 264 Engelhorn, E, and Wintz, H Munchen med Wchnschr, 1914, **61,** 689

6 Pottenger, F M Pulmonary Tuberculosis, 1908, William Wood & Co, New York

7. Titze Berl Tierartztl Wchnschr, 1912, No 30

or of phagocytosis healing is rather to be sought in the fixation of the bacilli by the tissues" Haupt[8] Schurr,[9] Citron[10] and other investigators have come to the conclusion that resistance to tuberculosis does not parallel the antibody concentration

If, then, tuberculin therapy is a valuable therapy, its effect probably depends on factors that are not related to the specific antibodies Bessau[11] has recently reviewed the subject in a helpful manner He calls attention to the fact that the tuberculin reaction is not related to our ordinary conception of specificity or immunity, because, in the first place, we cannot sensitize animals to tuberculin, secondly, that tuberculin contains no native protein — only polypeptids — and finally, that it has been practically impossible to transfer passively the sensitization of tuberculous animals to normal animals (Klopstock,[12] Landmann[13]) Hamburger had recognized the resistance that follows the repeated injections of tuberculin as an antianaphylactic phenomenon, nonspecific, independent of dosage, but depending rather on the reaction induced Bessau rightly emphasizes the differences between the general and local reactions to tuberculin, in progressive tuberculosis, for instance, the general reaction may become more pronounced while the local reactions may be extinguished, and vice versa While supposedly a method of active immunization, Bessau declares that the only effect is to produce a tuberculin resistance, which in a nonspecific way may be of benefit

Aronson[14] concludes as a result of the extensive investigations that he has carried out that the tuberculin reaction does not depend on antibodies, that the general reaction is not specific but is related to the disintegration of leukocytes about tuberculous foci, he concedes that there is an element of specificity in the cutaneous reactions This latter deduction he draws from his experiments with tuberculin digested with pepsin-hydrochloric acid This preparation was still able to induce a general but not a local reaction

To summarize the conclusions of the more recent workers the following would seem to be the concensus of opinion (*a*) the clinical course need not be influenced by the antibody concentration, (*b*) the tuberculin reaction does not depend on the antibody titer of the serum, (*c*) the general and local reactions are not comparable, (*d*) and tuberculin does not immunize, but the resistance to tuberculin established

8 Haupt, H Ztschr f Tuberk, **22,** 209, 363, 463
9 Schurr, J Deutsch Arch f klin Med, 1912, **109,** 112
10 Citron, J Deutsch Arch f klin Med, 1913, **110,** 184
11 Bessau, G Munchen med Wchnschr, 1915, **62,** 323
12 Klopstock, F Ztschr f exper Path u Pharmakol, 1914, **15,** 13
13 Landmann Deutsch med Wchnschr, 1912, **38,** 1245
14 Aronson, H Deutsch med Wchnsch, 1914, **40,** 487

during tuberculin treatment may possibly influence the existing tuberculosis in a nonspecific manner

Two further experiments firmly establish these deductions Bail showed that if a tubercle is implanted in a normal animal it at once reacts to tuberculin with a general reaction, that is, before either sensitization or immunization could possibly occur More recently Klemperer[15] has definitely excluded both the cellular and humoral antibody complex in the tuberculin reaction when he demonstrated that, when in animals the single tubercle is extirpated, the tuberculin reaction is extinguished at the same time This experiment is undoubtedly of primary importance

Before entering into a theoretical discussion of the possible mechanism involved it may be well to briefly review certain facts in regard to tuberculin The first of these concern the question as to the specificity of the reaction

SPECIFICITY

Feistmantel extracted an acid-fast streptothrix and obtained an active tuberculin On the other hand, leprous and actinomycotic patients are said to react strongly to tuberculin The tuberculous individual will react to many of the following substances injected either subcutaneously or intravenously with a typical tuberculin reaction and constitutional symptoms, while the nontuberculous individual will tolerate equal doses without reaction, these include the following Hypertonic salt solution, distilled water, iodids, some colloidal metals, protein split products, ferments, immune (tuberculous) serum, heterologous serums, exudates, photodynamic insults (heliotherapy, roentgen rays, deep red rays, etc)

Nor must it be supposed that this nonspecificity is limited solely to the general tuberculin reaction Tenzer,[16] for example, noted that in 73 children, of whom 48 reacted positively to the von Pirquet, 22 gave a comparable reaction with Witte peptone In another series of 69, of whom 34 reacted positively to the von Pirquet, 19 gave a reaction with cholera vaccine used in place of the tuberculin These nonspecific reactions occurred only in the von Pirquet positive children There is here distinct evidence that an increased susceptibility of the skin obtains which is wholly independent of specific factors Petersen[17] also calls attention to this fact, and Burnet[18] has studied the relation of the skin and general reactions in the lower monkeys, noting that while the general reaction might be positive in these animals during all stages of

15 Klemperer, F Beitr z klin d Tuberk, 1914, **30,** 431
16 Tenzer, E Monatschr f Kinderh, 1911, **10,** 131
17 Petersen, H Hospitalstid, 1912, **5,** 421
18 Burnet, E Compt rend Soc de biol, 1912, **72,** No 28

the disease, the skin reactions were negative throughout all stages of sensitization and disease Observations such as these led Torrenson[19] to use Witte peptone instead of tuberculin in the treatment of tuberculosis of the skin, his results, carried out on a limited number of patients, were satisfactory

Experiments carried out by Matthes[20] more than twenty years ago were along similar lines Matthes injected small amounts of albumoses into tuberculous guinea-pigs and found that a violent focal reaction occurred about each tubercle, followed by profound intoxication, loss of temperature and death in a short time In the normal animal only a slight and transient rise in temperature was observed These studies, really of the utmost importance in the study of the mechanism of the reaction, have been generally ignored

Probably of equal importance is the fact that the von Pirquet reaction is never augmented by immune tuberculosis serum when it is added to the tuberculin immediately before, or when incubated with the tuberculin before innoculation (the serum may be derived from immune animals or from patients in the various stages of the disease, with or without tuberculin treatment), but is invariably delayed when such serums are added (Petrova,[21] Aronson,[14] etc) The only activating substances are lipoidal in nature as described by Bing and Ellermann [22]

We are probably justified in concluding that the general reaction to tuberculin rests on factors largely nonspecific and that a nonspecific element enters also into the cutaneous tests When we turn to survey the factors that render the tuberculin reaction negative we find that this resistance is wholly nonspecific

INHIBITION OF THE TUBERCULIN REACTION

Von Pirquet observed that during measles and streptococcus infections the tuberculin reactions became negative, Brandenberg[23] found this to be true for scarlet fever, and Krannhals[24] as well as Glintschikow[25] observed the same condition in typhoid, pneumonia and acute articular rheumatism Cozzolino,[26] working with pertussis and Moltschanoff[27] with diphtheria and serum sickness, also observed this phenomenon The resistance to tuberculin during and following serum

19 Torrenson, E G Abst, Ztschr f Immunitatsforsch, 1912, **5,** 1020
20 Matthes, M Deutsch Arch f klin Med, 1894-1895, **54,** 39
21 Petrova, M K Abst, Ztschr f Immunitätsforsch, 1914, **6,** 1014
22 Bing, H J, and Ellermann, V Biochem Ztschr, 1912, **42,** 289
23 Brandenberg, F Deutsch med Wchnschr, 1910, **36,** 561
24 Krannhals Munchen med Wchnschr, 1910, **57,** 836
25 Glintschikow, W J Abst, Ztschr f Immunitatsforsch, 1916, **8,** 509
26 Cozzolino, O Abst, Ztschr f Immunitatsforsch, 1914-1915, **8,** 310
27 Moltschanoff, W T Jahrb f Kinderh, 1912, **75,** 434

reactions in children was confirmed by Luithlein[28] We are evidently dealing here with a general state of resistance to the local and in part the general tuberculin reactions during practically all the acute infections, during certain of the cachectic conditions, and following protein shock reactions (serum reactions)

In order to examine this relation to the problem before us we may revert to the second figure or curve in Chart 1 and study the material collected by Stern[29] Stern determined that 65 per cent of the women at his clinic (nonpregnant) gave a positive tuberculin reaction, that this percentage in the pregnant women decreased progressively to term and that immediately following delivery the percentage reacting positively began to increase until in women in the fifth and sixth day of the puerperium 67 per cent gave the reaction We have here definite evidence that a progressive resistance occurs during pregnancy and that this resistance vanishes in a surprisingly short period of time after delivery It will be observed in the chart how closely this relation parallels the rise in the antiferment titer Stern was familiar with the increase in the blood lipoid content during pregnancy[1] and suggested that the resistance was due to a binding of the antibodies to these lipoid bodies It is apparent from these observations that the resistance to the tuberculin reaction (both general and local) need not depend on specific factors as might be surmised were we to observe it exclusively following repeated tuberculin injections

EFFECT OF TUBERCULIN ON THE NONTUBERCULOUS ANIMAL

We are more or less familiar with the effect of tuberculin on the tuberculous organism and are apt to overlook the fact that tuberculin may develop marked reactions in the metabolism of the normal animal That this is the case has been demonstrated by Mircoli[30] Mircoli used tuberculin and also tubercle bacilli (killed) and injected these in small doses into normal experimental animals The injections were followed by a short negative phase (especially when the dose was large) during which time the animals lost weight as compared to the controls, this was followed by a longer period during which the weight of the treated animals increased over that of the control animals When repeated small doses were given, resistance developed, and the negative phase diminished, the animals showing a decided gain in weight as compared with the untreated animals

28 Luithlein, F Wien klin Wchnschr, 1914, **27**, 493
29 Stern, R Ztschr f Geburtsh u Gynak, 1910, **66**, 532
30 Mircoli, St Pathologica, 1914, **5**, 118

THE DIRECT EFFECT OF TUBERCULIN ON AUTOLYSIS

Finally, it has been observed that tuberculin can influence autolytic processes directly Pesci[31] added tuberculin (and other toxins) to autolyzing organ emulsions and found that the rate and magnitude of the process was increased in a degree proportional to the amount of tuberculin added This effect seems to have some relation to the lipoids of the substrate It is known that the lipoid solvents, including alcohol, will, when added to autolyzing organs, reduce the latent period of autolysis, presumably by destroying a lipoid-protein combination that normally resists autolysis (Chiari[32]), and which, under ordinary conditions, is only destroyed when a sufficient degree of acidity has developed Pesci observed that in his tuberculinized substrate the neutral fats and fatty acids tended to decrease within fifteen minutes while the soaps increased, as compared to the normal autolysis Barlocco[33] observed a similar lipoid rearrangement during autolysis when diphtheria toxin had been added to the substrate

THEORETICAL CONSIDERATIONS

The facts which have accumulated as a result of both experimental and clinical investigation make it apparent that we must seek an explanation along lines not necessarily associated with the usual conception of immunity In the first part of this paper evidence has been presented which indicates that the proteolytic ferment and the antiferment exercise a considerable influence on the tuberculous process Is it possible that changes in the ferment-antiferment balance may be responsible for some of the phenomena observed in the tuberculin reaction?

We must keep in mind that tuberculin is not a native protein, but consists largely of polypeptids and must essentially be a toxic substance, as Turban says "A preparation which is nontoxic and yet potent, is unknown" There is evidence that the activity of the various tuberculins is in proportion to their surface tension, which, in so far as tissue effect is concerned, simply means that the more diffusible products are the more toxic[34]

In its essentials the tuberculin injection might be supposed to lead to the changes which we associate with the typical protein "shock" reaction, that is, it would result in (*a*) a mobilization of the proteolytic ferments, (*b*) in a primary reduction followed by a subsequent increase in the antiferment titer, and (*c*) in the development of a non-

31 Pesci, G Pathologica, 1911, **3**, 144, and Zentralbl f Bakt, Part 1, Orig, 1911, **59**, 186

32 Chiari, Rich Arch f exper Path u Pharmakol, 1908-1909, **60**, 257

33 Barlocco, A Pathologica, 1911, **3**, 7

34 Kollert, Victor Beitr z Klin d Tuberk, 1914, **30**, 173

specific resistance comparable to the "antianaphylaxis" or the "desensitization" of the immunologist Graphically, these changes can be illustrated as in Chart 3, that is, following the injection we might expect a period when proteolytic activity is favored — lowering of the antiferment and increase in the protease — followed by a zone of several days' duration during which time the reverse holds true During this latter time the ereptase might be augmented, which theoretically would aid in detoxication by eliminating the higher split products

We know that the use of small doses of tuberculin at definite or varied time intervals has been established in routine as the result of a vast accumulation of clinical experience, largely empirical, and we are

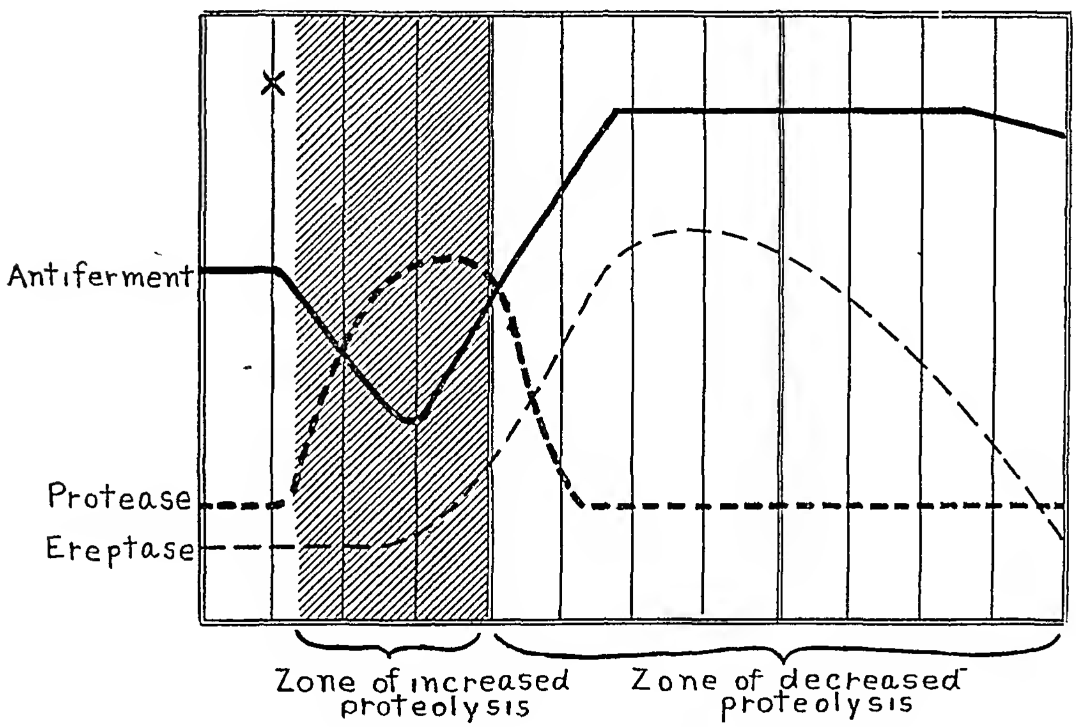

Chart 3—Schematic relation of serum ferment and antiferment following tuberculin injection

justified in believing that it represents the most favorable method of its use With this method we can undoubtedly produce a tuberculin resistance or tolerance in the tuberculous individual, that is, as the result of repeated stimulation of this kind the organism becomes more and more resistant to intoxication It has been the general impression that, because anaphylactic phenomena are so strikingly specific, the resistance following shock is equally specific This, however, is not true The most recent work, especially that of Bessau and his associates,[35] has shown that antianaphylaxis is practically nonspecific The state of desensitization, or the refractory period following anaphy-

35 Bessau, G, Opitz and Preusse, O Zentralbl f Bakt, Part 1, Orig, 1914, **74**, 162, 310

lactic shock, occurs also following the injection of anaphylatoxins and similar protein poisons, Vaughn noted the same general phenomenon when injecting his protein split products, repeated sublethal doses increasing the resistance until one or possibly two times the fatal dose could be tolerated

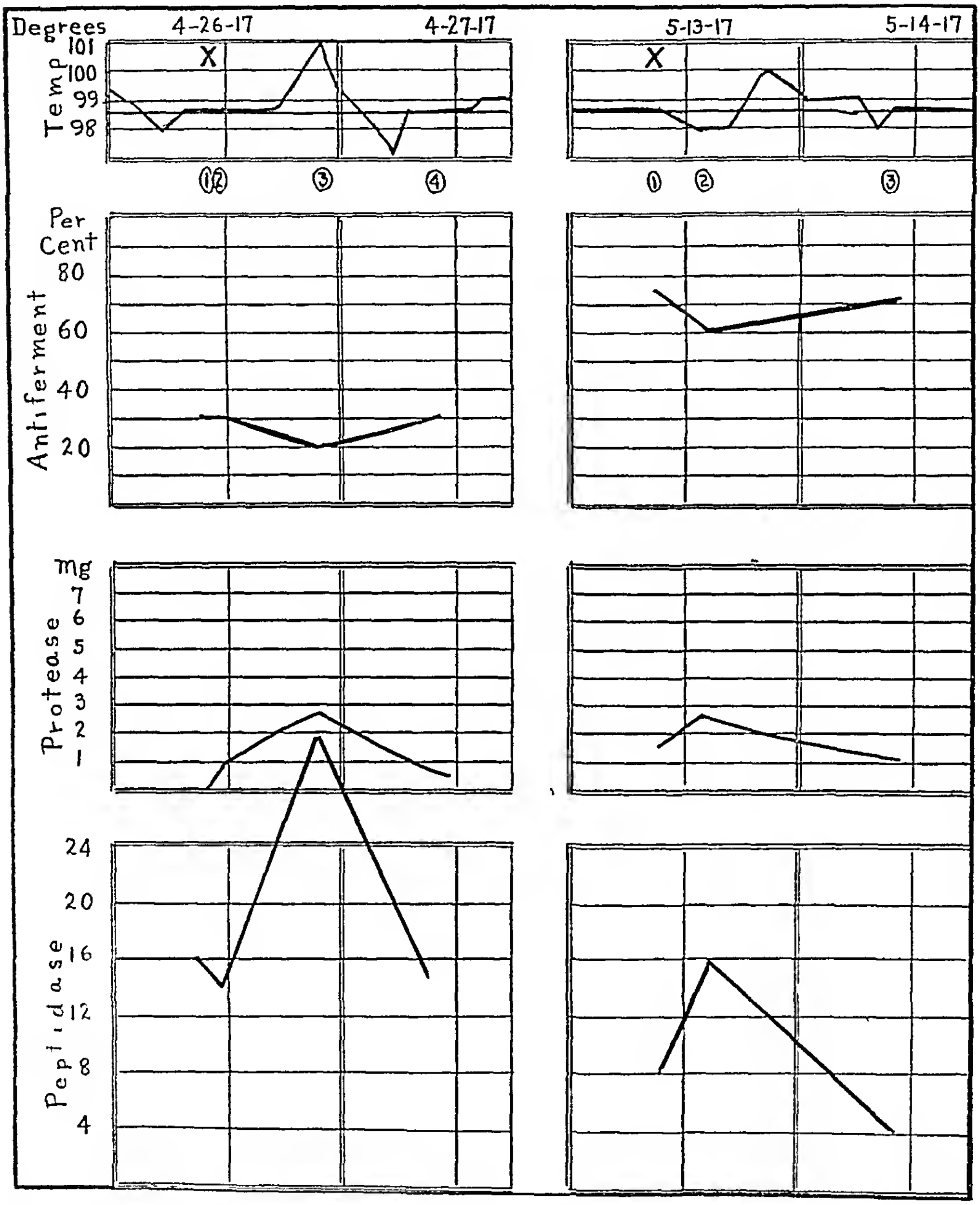

Chart 4—Effect of tuberculin injection on serum ferment and antiferment

It had been observed, first by Rusznjak[36] that the serum antiferment titer was markedly augmented after anaphylactic shock, to which fact Rusznjak in part attributed the increased resistance to the refractory

36 Rusznjak, S Deutsch med Wchnschr, 1912, 38, 168

period Jobling[37] made similar observations following a variety of protein shock poisons and showed, furthermore, that when the antigen was mixed in vitro with an antiferment before injection into the animal, anaphylactic shock could in many instances be averted It seems reasonable at any rate to assume that where we are dealing with an intoxi-

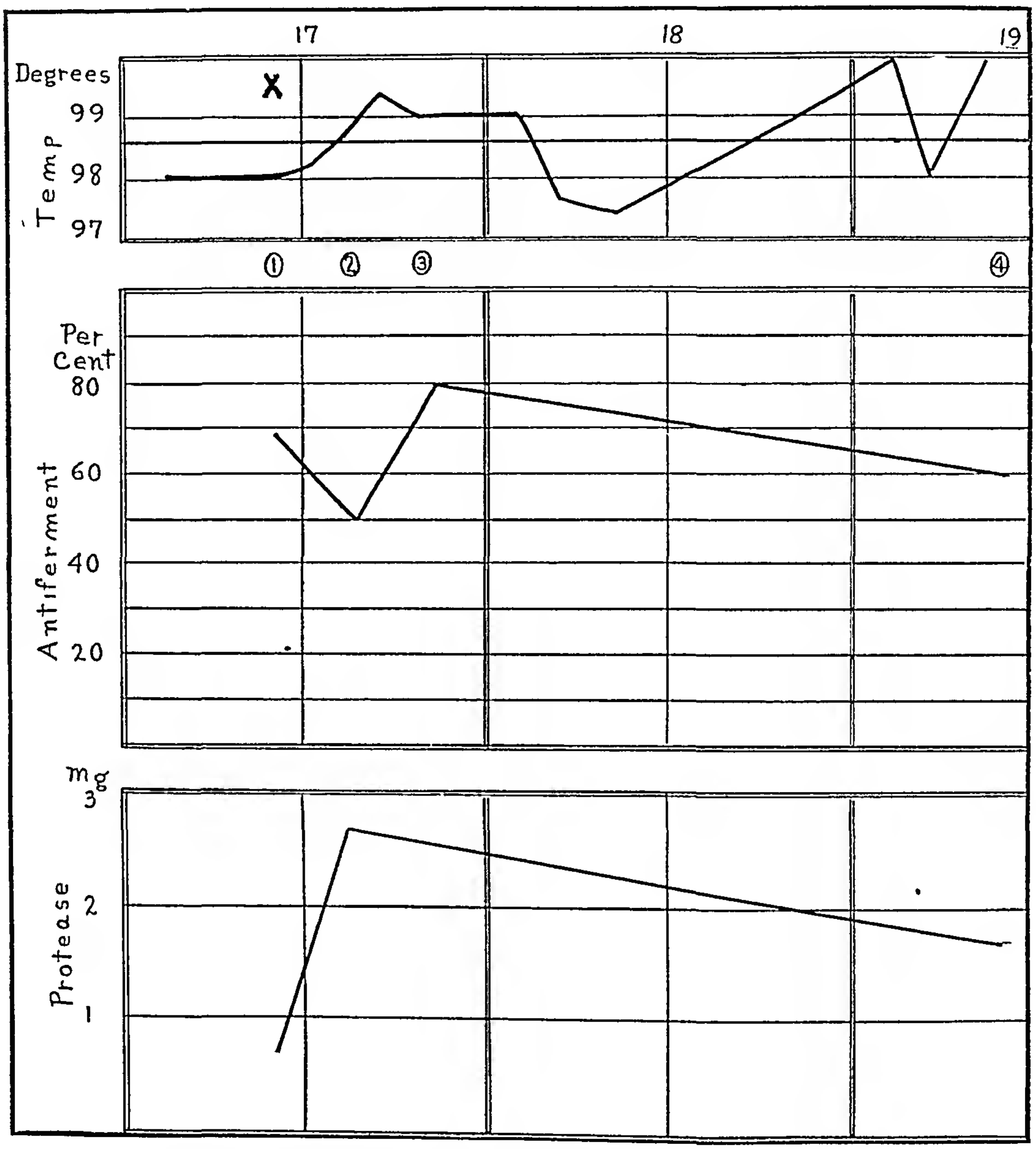

Chart 5—Serum alteration following tuberculin injection

cation having its origin in protein splitting in the body, an increase in the antiferment, that is, in those substances which inhibit or delay proteolytic activity, would be one of the factors involved in this resistance

We could assume that the tuberculin reaction takes place somewhat as follows When tuberculin is injected subcutaneously a certain number of cells are injured and some protease is liberated This, just as it

37 Jobling and Petersen Jour Exper Med, 1914, **20**, 468

takes place physiologically during the menstrual period, is carried to the tuberculous focus, and, by digestion there, produces the typical focal reaction and with it a liberation of toxic material and general malaise We must keep in mind, too, the possibility of the direct activating influence of the tuberculin on autolytic processes At any rate we deal not with a condition of sensitization of the tissues of the body as a whole, but solely with the slight breaking down of tuberculous tissue at some point, the degree depending on the relative amount of ferment mobilized, on the relative vascularization, and on the amount of connective tissue that protects the focus Thus, the reaction would be negative in the nontuberculous, for here, when a ferment mobilization does occur it finds no pathologic focus to attack, no protein is broken down and no febrile reaction occurs In the tuberculous patient we have, furthermore, a cumulative effect when the ferment-antiferment balance is altered, because the liberated toxic material will add a secondary protein shock which is lacking in the normal person

While it is apparent from these considerations that we may be dealing with a reaction that is nonspecific, in that the means used to elicit it are not specific, it is immediately apparent that the reaction itself resulting from the stimulation of the tuberculous focus implies a specific stimulation in the true sense of the term, in that disintegrating bacilli, and possibly even living bacteria, are absorbed from the focus, whether that focus is stimulated as a result of heliotherapy, of immune serum, of iodin or of tuberculin As far as immunologic investigation has gone it seems certain that immunization brought about as the result of the incorporation of whole organisms, either living or dead, has given the most satisfactory results in protection experiments It is essential at any rate to keep in mind this dual effect of the tuberculin reaction, the specific phenomena following in the wake and as a result of the effect of the nonspecific reaction

REPORT OF EXPERIMENTAL CASES

Case 1—F L, male, white, aged 18 years, had tuberculosis of the kidney (kidney removed six months previously) Cystoscopic examination revealed tuberculosis of the bladder There was no active pulmonary involvement One mg old tuberculin was given subcutaneously at 10 a m Serum taken at 10 and 11 a m, 10 p m and 10 a m the following day The examination of the serum revealed the changes in the ferment titer charted in Chart 4, A

It will be noted that the antiferment titer was diminished by evening, when the maximum temperature was recorded The protease increased from 0 to 0 27 mg per c c during this time, while the peptidase, which was originally fairly strong, increased to about twice the original titer This increase was not maintained the following day Two weeks later a second injection (2 mg O T) was made and similar serum alterations followed this injection (Chart 4, B)

Case 2—H V, man, white, aged 52, had unilateral pleurisy with a large amount of hemorrhagic exudate, which was withdrawn by puncture The clinical course was afebrile, with occasional periods of temperature to 100 F for one or two days He was given 1 mg O T subcutaneously. No increase

of temperature was observed, but considerable malaise and headache followed The serum alterations have been recorded in Chart 5 There was a distinct decrease in the antiferment for several hours after the injection, then a slight increase in the evening The protease increased following the injection No clinical effect was observed from the small dose used

For comparative purposes the following two cases are of interest

CASE 3—J R, a white man, aged 45 years Physical findings revealed bilateral pulmonary involvement with cavity formation, but absence of tubercle bacilli in the sputum There was a considerable range of temperature, marked cough and expectoration He was given 1 mg O T subcutaneously This

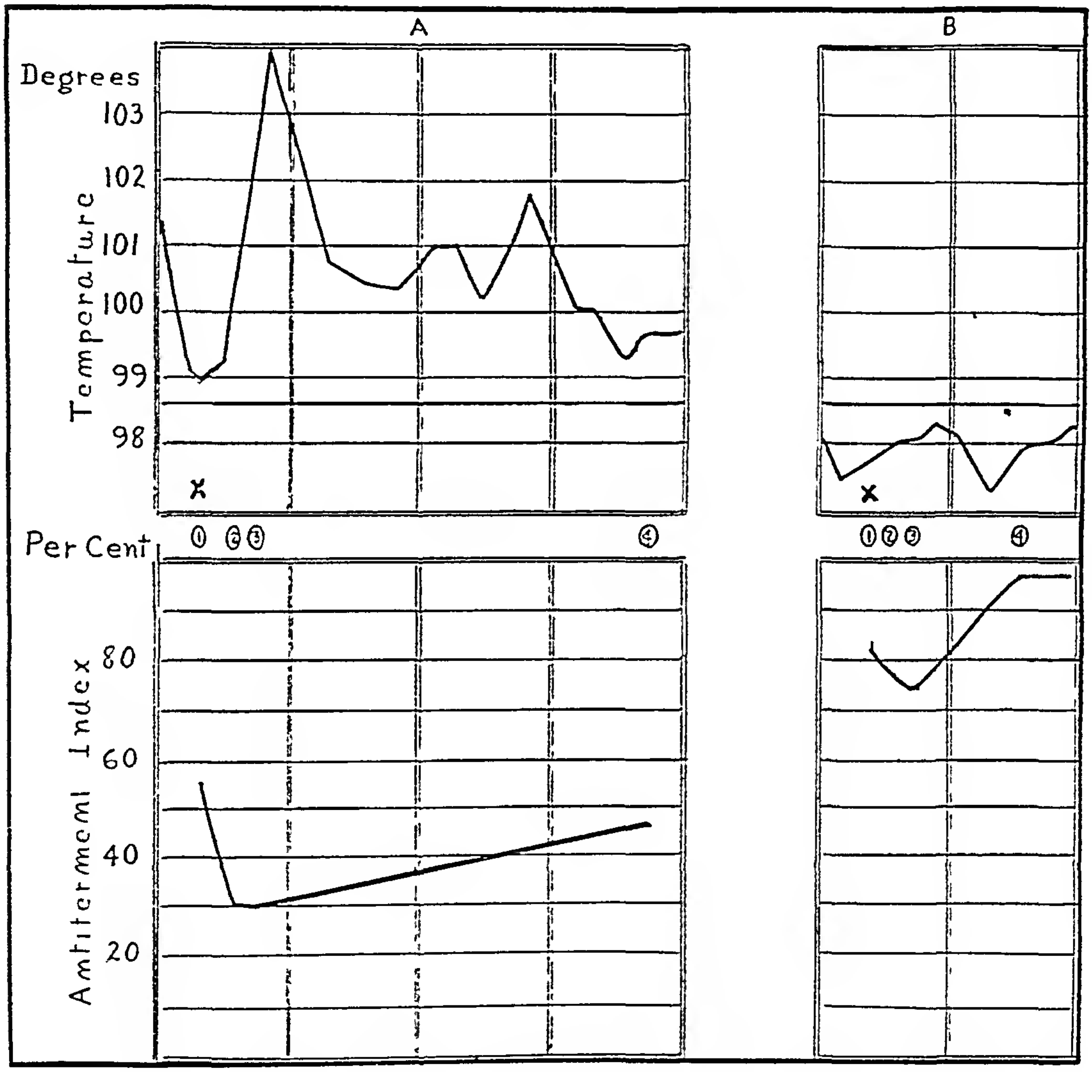

Chart 6—Antiferment alteration in case unfavorably (*a*) and favorably (*b*) influenced by tuberculin

was followed by a rise in the temperature as well as physical findings of focal activation, which continued for several days Clinically this patient was not improved after the injection, indeed, the general feeling of malaise and discomfort seemed increased

When the antiferment curve is examined (Chart 6, A) it will be observed that the decrease persisted for a considerable time and even after three days had not returned to the original titer When contrasted with the following case this fact is of interest

Case 4—F B, a white man, aged 40, with arrested bilateral apical lesions and general visceroptosis, entered the hospital because of gastric distress The temperature curve was persistently subnormal He was given 2 mg O T subcutaneously, followed by no temperature or constitutional effect It will be noted that the antiferment (Chart 6, B) after the initial decrease, reached a level that was considerably higher than before the injection

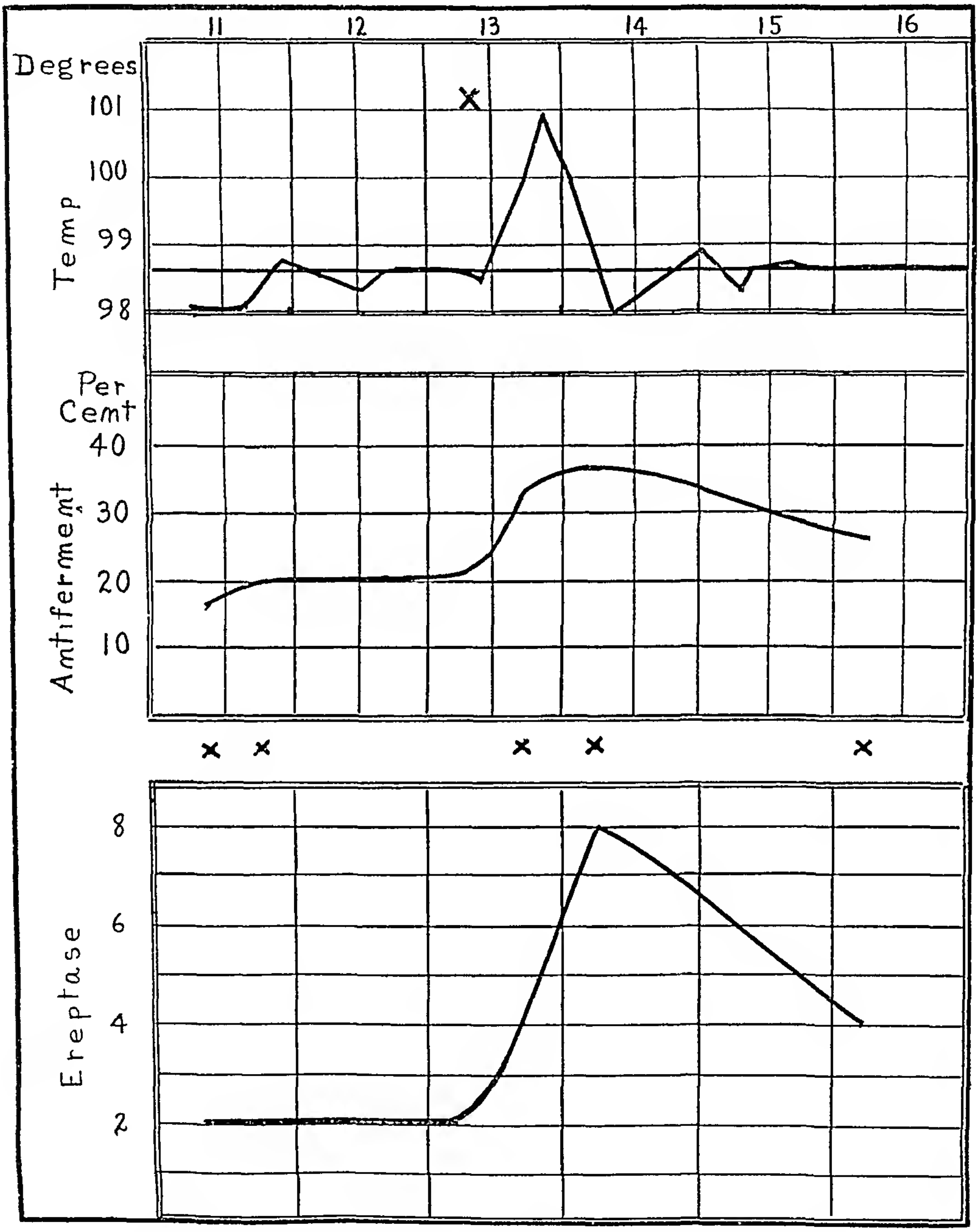

Chart 7—Serum alteration following tuberculin injection

The serum changes that occur following the injection in a fairly active case with well defined clinical improvement following the injection are illustrated in Chart 7

CASE 5—O V, a white man, aged 24, had tuberculosis of the peritoneum He entered the hospital with a considerable febrile temperature range, emaciated, and with a large exudate in the peritoneal cavity, which was removed at two separate times With rest the patient improved progressively until the temperature remained practically normal At this time he was given 1 mg O T subcutaneously which was followed by a sharp temperature reaction (101 F) Blood samples had been collected at several periods previous to the injection, they were also taken in the evening of the day of injection, the following morning and on the third day following

It will be observed that the antiferment increased considerably and that the rise persisted for at least three days after the injection The protease was not determined but the ereptase increased after the injection and continued at a high level for the day following The patient said he felt improved, and objectively seemed so

In several syphilitic cases the serum alterations following the tuberculin injection (2 to 5 mg O T) have been similar in character

In fifteen cases in which the serum reaction has been studied following tuberculin injection, of which the charted cases are representative, either one or more of the ferment-antiferment changes suggested as possibilities in the theoretical discussion, have been observed The decrease in the antiferment has been found to be the most constant alteration, in the cases unfavorably influenced by the tuberculin no increase followed the original decrease, in the cases clinically improved a well-marked rise usually follows The changes in the ferments—protease and ereptase— are less constant, but usually at least one of these ferments makes its appearance, the ereptase in particular being increased in the cases which give evidence of benefit from the reaction

It might seem warranted to consider the tuberculin reaction as a two-phase phenomenon in the tuberculous individual The primary alteration of the ferment-antiferment balance brings about a medium favorable for proteolysis in and about the tubercle Digestion and the liberation of toxic material result and are reflected in the constitutional effects In the nontuberculous individual it is probable that the primary serum alterations also occur, but the digestive ferments, finding no focus to attack, liberate no toxic material and no general reaction is elicited

CORRELATION

From the evidence presented it seems probable that the ferment mobilization, however produced, will influence the tuberculous focus and bring about a general reaction if the digestion be of sufficient degree From this point of view we can understand the undeniable lack of specificity associated with the general reaction, any agent that will bring about a ferment-antiferment balance favorable for proteolysis will effect a general reaction provided the focus be sufficiently unstable That the various vaccines, protein split products and even

inert physical agents will do this has been demonstrated[38] Similarly, Pfeiffer[39] observed such changes following burns of varying intensity, making it apparent why, when a patient during the course of heliotherapy burns to a moderate degree, a tuberculin reaction with focal and general effects may result Conversely we can understand that in any infectious granulomas in which a balance exists similar to that obtaining in the tubercle, the injection of tuberculin will be followed by a marked febrile reaction

If we assume that proteolytic factors enter also into the local cutaneous reactions, then an increase in the antiferment would operate to oppose such a reaction and render it negative This seems evident when we keep in mind the increase in the antiferment that takes place during the course of a physiologic process (pregnancy), during disease (acute infections) and following induced protein "shock" or tuberculin reactions, and the inhibition of the tuberculin reactions during these conditions In the late stages of tuberculosis this same increase in antiferment is observed (coincident with the decrease in the lipases Marutaew,[40] Bauer[41]), and the local reactions to tuberculin become less evident while the general reaction may become more severe because of the lability of the numerous foci The participation of the proteolytic ferments in the local reactions is also made probable in that any antiferment added to the tuberculin before its local application (sodium oleate and serum) will invariably delay the reaction The recent work of Sherrick,[42] of Stokes[43] and of Burroughs and Neymann[44] will, however, probably materially modify our present conception of skin reactions, so that any discussion at present is out of question in this particular domain Sherrick observed that he could obtain a positive luetin reaction in all iodized patients, and that the injection of agar and starch gave a reaction as well He noted that a patient who under normal conditions reacted to the luetin with a diffuse areola went on to complete pustule formation under iodids This work has been repeatedly confirmed[45] For reasons given early in this paper we assume that the iodin and iodid act therapeutically, by lowering the antiferment of the blood and tissues when given in gradually increas-

38 Jobling, Petersen and Eggstein Jour Exper Med, 1915, **22**, 597

39 Pfeiffer, H Ztschr f Immunitatsforsch, Orig, 1915, **23**, 473

40 Marutaew, A S Abst, Ztschr f Immunitatsforsch, 1913, **7**, 90

41 Bauer, J Wien med Wchnschr, 1913, **36**, 2197

42 Sherrick, J W The Effect of Potassium Iodid on the Luetin Reaction, Jour Am Med Assn, 1915, **65**, 404

43 Stokes, J H Jour Infect Dis, 1916, **18**, 402

44 Burroughs, M T, and Neymann, C A Jour Exper Med, 1917, **25**, 93

45 Kolmer, J A, Matsunami, T, and Broadwell, S The Effect of Potassium Iodid on the Luetin Reaction, Jour Am Med Assn, 1916, **67**, 718 Kolmer, J A, Matsunami, T, and Immermann, S, and Montgomery, C M Jour Lab and Clin Med, 1917, **11**, 401

ing doses,[46] and from this point of view the observations made by Sherrick and others are readily understood, in that a lowering of the threshhold of proteolysis would bring about a condition when instead of the luetin producing a simple inflammatory reaction, the process would go on to complete pustule formation and necrosis when the antiferment "brake" was released The observation of Burroughs and Neymann is of equal importance in that they have demonstrated that amino-acids in sufficient concentration may be toxic for cells Inasmuch as the rate of diffusion in the cutaneous tissues is slow, it is readily understood that a sufficient concentration of such lower split products might accumulate and result in toxic manifestations quite different from those observed when dealing with the organism as a whole

The alterations following tuberculin therapy probably bring with them two general effects (*a*) the rate of nitrogen metabolism is decreased and a storage of nitrogen may result, as indicated in the work of Mircoli, (*b*) the reaction, even if local and without apparent constitutional effect, increases the antiferment gradually and in this way not only increases the resistance to following injections, but increases the resistance at the focus against digestion and intoxication

With this idea in mind one can understand why many clinicians have, as a result of clinical experience alone, come to realize that in tuberculin therapy they are not dealing with a specific effect and are not primarily immunizing the patient against the tuberculous infection The nonspecificity of the reaction that follows tuberculin injections has recently been taken advantage of by Browning[47] in dealing with patients highly susceptible to tuberculin, who nevertheless insisted on tuberculin treatment In such cases Browning has found that by interpolating several doses of typhoid and other vaccine, he was able to increase the following tuberculin doses very materially without undue reaction on the part of the patient

It is interesting to recall in this connection that tuberculin can be used interchangeably, to a certain degree, with other agents that bring about an alteration in the ferment-antiferment balance and thereby induce therapeutic effects One needs but mention the use of tuberculin in syphilis (Biach[48]) and the effect said to be noted in paresis (von Wagner[49]) The results of von Wagner have been confirmed from many sources (Dollken,[50] Battistessa[51] and Jukow[52]) We have, fur-

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46 Jobling and Petersen The Therapeutic Action of Iodin, The Archives Int Med, 1915, **15**, 286

47 Browning, C C Los Angeles (Personal communication)

48 Biach, M Wien klin Wchnschr, 1915, **28**, 1345

49 Von Wagner Wien med Wchnschr, 1909, **59**, 2125

50 Dollken Berl klin Wchnschr, 1913, **50**, 962

51 Battistessa, P Riv ital di Neuropatol psichiat ed elettroter, 1912, **5**, 117.

52 Jukow, N A Abst, Ztschr f Immunitatsforsch, 1913, **7**, 558

thermore, to keep in mind the well-known phenomenon of the activation of tuberculous lesions in diseases associated with an increased amount of proteolytic ferments in the serum, as, for instance, in dementia praecox and in carcinoma, Lubarsch having called attention to this latter fact

ANIMAL EXPERIMENTATION

Inasmuch as practically all of the experimental work in tuberculosis has been done on the smaller experimental animals (guinea-pigs and rabbits) it may be well to discuss briefly the relation of the serum ferments in these animals and the effect on the tuberculosis problem

Guinea-pig serum (and also rabbit serum, to a lesser degree) differs widely from the human in containing much less antiferment, more lipase and vastly more proteolytic ferment — both protease and ereptase Under such conditions we should expect that the connective tissue fixation and encapsulation would be made more difficult because of the pronounced digestive effect of the serum On the other hand, abscess formation might be expected to lead to caseation even with nontuberculous processes (the leukocytes of the guinea-pig contain no leukoprotease) if the permeability of the focus is not sufficient to permit the free entrance of serum These are of course the actual conditions to be observed in pathologic conditions in these animals and constitute one of the chief reasons why the results of animal experimentation cannot be applied with any degree of certainty to the tuberculosis of man

It is only when serum alterations are produced in the guinea-pig so that it resembles the condition in man that the picture of the tuberculous process offers a similarity to that of the human form Helen Baldwin and Elise L'Esperance[53] have recently published observations that are of interest in this connection By producing an occasional protein shock (with typhoid vaccine) they found that the treated animals gained in weight over the control animals, and that the tuberculous lesions showed a marked fibrosis, an appearance quite unusual in the tuberculosis of these animals The results are probably to be accounted for by the decided increase in the antiferment following such typhoid injections, which would tend to preserve the connective tissue encapsulation and thus aid in the fixation of the bacteria

Experiments such as these serve to bring out the fact that a sharp difference exists between an immunity against the establishment of an infection and the resistance to an infection already established The guinea-pig, practically immune to spontaneous tuberculosis, possibly just because of the abundance of the serum ferments, by this very fact is enabled to offer little resistance once the infection is established,

53 Baldwin, Helen, and L'Esperance, Elise Jour Immunol, 1917, **2,** 283

because the unfavorable serum balance prevents the fixation of the bacteria by connective tissue Under such conditions immunization per se will have no practical effect on the development of an established infection, whereas a protein "shock" reaction as carried out by Baldwin and L'Esperance does seem to influence the pathologic picture to a considerable degree, offering one of those instances in which therapeusis along nonspecific lines may possibly offer more benefit than therapy carried out with strictly specific end objects

THE RELATION TO THERAPEUSIS

The probable basis for the therapeutic effect of tuberculin has been discussed along the lines of the ferment alterations Clinical use has varied from overindulgence to underindulgence, with the final establishment of the small dose in ordinary routine There is, however, some evidence that occasional larger doses, with constitutional effects, may in certain instances be of greater benefit than the continual use of the very minute doses commonly in use Such authorities as Bandelier and Roepke,[54] for instance, call attention to the feeling of well being and the objective clinical improvement that may follow such a general reaction in some individuals The difficulty in predetermining just which cases may so react probably makes the current method of administration more suitable for routine use

It may be of interest to note in how far more or less established empirical therapeusis has followed along lines that influence the ferment-antiferment balance This can be divided into two general groups, the first having to do with fats and lipoids of various kinds Czerny[55] in a very interesting paper has presented evidence that the immunity of the nursing infant to many of the ordinary infections is not due to immune bodies furnished in the milk of the mother, but is closely related and dependent on the fat constituents of the milk, which in some manner augment the resisting power of the infant Among empirical remedies used in tuberculosis, fats have played a large rôle, including the highly unsaturated fish oils, milk, cream and the yolk of eggs, the use of phosphorus must be included in this category[56] In the consideration of the value of just these substances it is interesting to recall that Fermi[57] noted the antiferment property of milk and eggs many years ago, and it can be demonstrated experimentally that the antiferment of the lymph is gradually increased after a meal of milk

54 Bandelier and Roepke Lehrbuch der spec Diag u Therap d Tuberk, Ed 8, Wurzburg, 1915

55 Czerny Med klin, 1913, 895

56 Frank, L, and Schloss, E Jahrb f Kinderh, 1914, **79,** 539

57 Fermi, C Centralbl f Bakteriol, Part 1, Orig, 1909, **50,** 225

Braunstein and Kepinow[58] found that phosphorus increased the antiferment, and the increase in the antiferment following the continued use of the unsaturated oils seems logical considering the probable constitution of the antiferment lipoids The feeding experiments of Weigert[59] are also of interest in this connection

It is not within the range of this paper to discuss the relation of the lipases to the tuberculous infection, although the subject is intimately bound up with this particular phase of therapy and as such has been discussed by the Russian workers,[60] who seem to have devoted considerable study to the therapeusis of tuberculosis by means of the fat substances Briefly, this therapy might be described as a method to increase the antiferment, to check proteolysis at the focus, and aid in the conservation of the connective tissue of the scar

The second school, the foremost advocates of which we find among the French clinicians, has placed greater reliance on iodin and its compounds, but chiefly on free iodin[61] Apparently such therapy has decided value in glandular tuberculosis, and with apparent reason By this method of therapy the antiferment is probably reduced[46] and the connective tissue reaction about the focus lessened so that a slow and gradual exposure of the focus follows If this focus be in lymphatic tissue where lipolytic activity is provided by the lymphocytes, the tubercle bacilli are probably destroyed when they are exposed to such activity, if the focus is in pulmonary or other nonlymphatic tissue the effect of the iodin may simply be in the nature of an autotuberculinization, in which digestion is first aided, then checked by the antiferment reaction that follows the digestion Theoretically, this seems ideal therapy in the early case in which the body is able to withstand a certain amount of intoxicating material gradually absorbed

If in this paper certain of the ferment and antiferment changes have been dwelt on, it has not been done with the idea that they represent the exclusive factors that effect the tubercle in its relation to the host The digestive factors are at best but one of the many complex balances that have a rôle in the adjustment of the infected organism to the parasite, but having such a rôle, it may be well to keep the effect of these ferments and the antiferment in mind when we wish to study the effect of therapeutic measures on the pathologic process

58 Braunstein and Kepinow Biochem Ztschr, 1910, **27**, 170
59 Weigert Berl klin Wchnschr, 1907, **44**, 1209
60 Metalnikow, S J Ztschr f Immunitatsforsch, Orig, 1914, **22**, 235
61 Barbier Ztschr f Tuberk, 1914, **22**, 433

LIPODYSTROPHIA PROGRESSIVA *

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The term "lipodystrophia progressiva" was first applied by Arthur Simons to a syndrome as described by him,[1] in 1911

This condition is rather uncommon Up to the present about twenty-four cases have been reported and the only case in American literature I have been able to find has been published by Herrman [2] The most recent and comprehensive review of this subject is by F Parks Webber,[3] who has collected all the reported cases and clearly discusses this condition, its probable causes, its course, the outlook in the various cases, and has reviewed them up to the time of his article and also several cases with which he was familiar but which had not yet appeared in the literature

Lipodystrophia progressiva is a term applied by Simons to a syndrome beginning most frequently between the fifth and twelfth year, and chiefly affecting females In this condition, there occurs a gradual, progressive emaciation, beginning in the face and progressing downward, involving the neck, shoulders, trunk and upper extremities, with, in most reported cases, an increased deposit of fat in the buttocks, thighs and — sometimes — the legs The gradual disappearance of fat progresses until the appearance of the face is most characteristic The cheeks become sunken, the eyes deeply set, the malar eminences prominent, the temporal regions sunken When the patient smiles, the cheek is thrown into deep folds and the face generally has a cadaverous appearance The neck becomes thin, the clavicles and scapulae extend prominently forward The intercostal spaces are well marked, the breasts are pendulous and, owing to the disappearance of the fat, hard and nodular

In contrast to this wasted appearance of the upper extremities and face, below the line of the iliac crests the individual presents a plump appearance, in some of the reported cases, even amounting to grotesqueness

Usually, the attention of the family is first called to this condition by the emaciation which takes place in the face, and the fear of some

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1 Simons, Arthur Ztschr f d ges Neurol u Psychiat, Berlin, 1911 (Originalien)

2 Herrman, Charles Progressive Lipodystrophy, THE ARCHIVES INT MED, 1916, **17**, 516

3 Webber, F Parks Quart Jour Med, 1916-1917, Nos 37 and 38, p 131

disease prompts them to seek medical advice The patients themselves complain little or not at all In the advanced cases, there is sometimes a complaint of a feeling of chilliness and excessive perspiration, in other cases, a weakness or nervousness

Fig 1—Author's patient at the age of 5

The condition, in all reported cases, progresses for a certain time and then seems to be arrested The ages, in reported cases, vary from 6 or 8 years to 39, the latter being the case of M Laignel-Lavastine and Viard [4]

Fig 2—Author's patient at the age of 8

In all the cases there is a gradual progression of the emaciation of the face, upper extremities and trunk and increase in size of the lower extremities over a period of ten to twenty years, after which there is spontaneous arrest

4 Laignel-Lavastine and Viard Nouv iconog de la Salpetriere, 1912, **25,** 473 (with plate)

In the two cases reported by J Husler[5] which occurred in males beginning in early childhood, there was no corresponding increase in the size of the lower extremities It seems to be the opinion of most of those who have reported these cases that this increase in the deposit of fat in the pelvic region and lower extremities is rather a characteristic of the female sex It is my opinion that this characteristic is accentuated by the efforts made to overnourish the patient to counteract the wasting which takes place in the upper portion of the trunk, face, etc

Much speculation has resulted as to the cause of the condition one author regarding it as secondary to tuberculosis, others as being the result of abnormal functioning of the sympathetic system Most authorities think there is some relationship between this condition and

Fig 3—Author's patient at the age of 10

abnormal functioning of the endocrine glands It would, however, appear to me that this condition is closely related to the muscular dystrophies, that here one deals with dystrophy of fat tissue and in the latter, a dystrophy of muscle tissue If this be the case, we are dealing with an abiotrophy The condition does not seem to influence the duration of life Examination of the skin and subcutaneous tissue in the emaciated areas shows the only pathologic change that has taken place to be an almost complete disappearance of fat

Microscopically, traces of fat are found in the sebaceous glands and around the hair roots In Simons' article[6] there are most excellent illustrations in which there is a comparison made between the sections of skin taken from the patient suffering from lipodystrophia progressiva and a markedly emaciated patient suffering with tuberculosis

5 Husler, J Ztschr f Kinderh, 1914, **10,** 116
6 Simons, Arthur Ztschr f d ges Neurol u Psychiat, 1913, **19,** 377

These illustrations show very clearly that even in the most emaciated individual there still remains some fat which can be readily demonstrated microscopically beneath the skin, whereas in a patient with lipodystrophia progressiva, there is practically an entire disappearance of fat in this same region

Lipodystrophia progressiva must be differentiated from emaciation due to diseased conditions, such as tuberculosis, cancer, intestinal disease, nephritis, cardiovascular diseases, etc This can readily be done by proper examination It must be differentiated from facial hemiatrophy, from the emaciation that may occur in hyperthyroidism, at puberty, in the period of lactation, the menopause, etc

Fig 4—Front and profile face views of author's patient

Usually, if this condition is thought of and proper examination made, there is little difficulty in its diagnosis The condition is slowly progressive and is limited to the fatty tissue of the face, neck, upper extremities and trunk, the muscles, bones, skin, vascular system, etc, not being affected

The outlook as to life in these cases is extremely good, death, when it occurs, being due to some intercurrent condition The condition usually advances for a number of years and then there is a spontaneous arrest It does not interfere with the functional capability of the various organs or with physical or intellectual activity

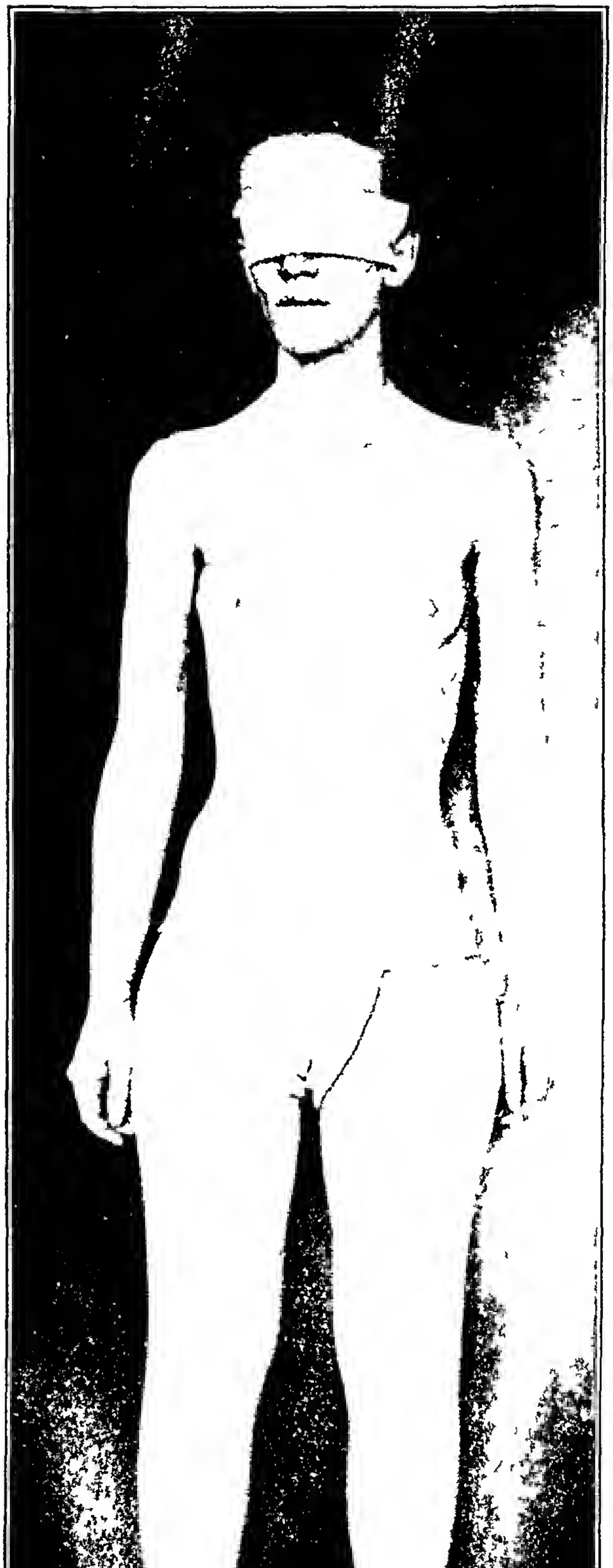

Fig 5—Front view showing emaciation of face, trunk and arms, and plump condition of hips, thighs and legs

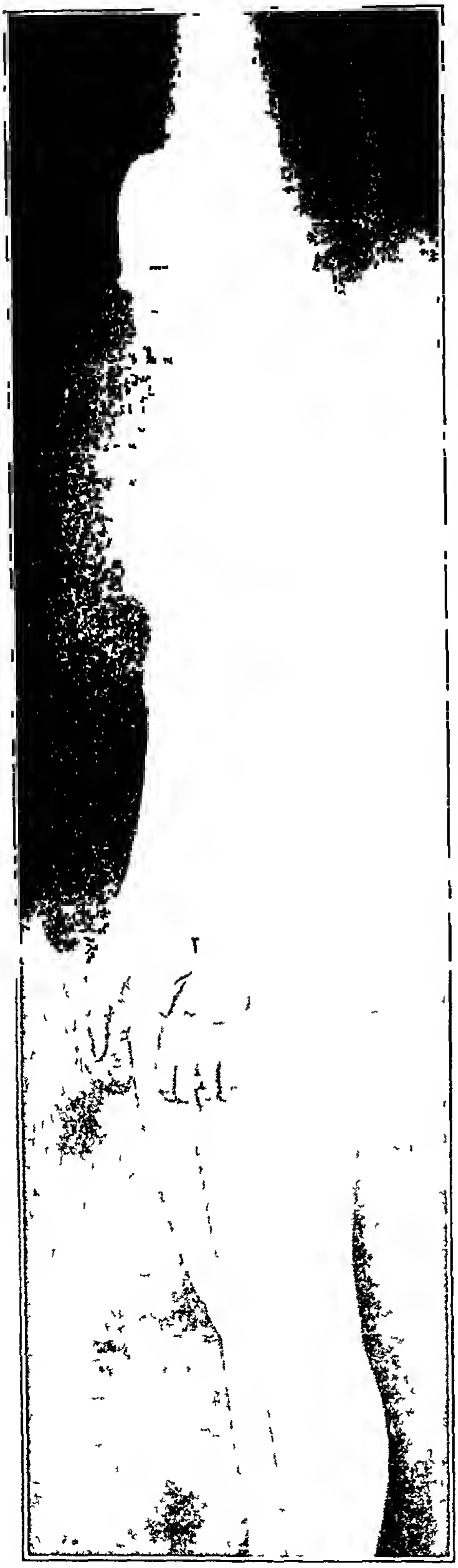

Fig 6—Lateral view of author's patient

Fig 7—Back view

The case reported by Herrman[2] existed for many years The patient married and had several healthy children Apparently, the chief objection to the condition is a cosmetic one In the first case reported by Simons[1] the condition occurred in a dancer, and owing to the marring of her facial attractiveness, it interfered with her livelihood

All sorts of treatments have been tried the administration of the various glandular extracts, massage, electricity, tonics, overfeeding, hydrotherapy, etc It would seem as if they were of but little use in allaying the progress of the condition After a time, there occurred a spontaneous arrest For cosmetic purposes, the injection of paraffin, fats and the transplantation of fat have been employed (Hollander[7])

REPORT OF A CASE

The patient, T M, aged 15, a schoolgirl, was seen in consultation with Dr R Tunstall Taylor, and examined in May, 1917

The patient has the facial appearance of a very much older woman She complains of a change in her facial appearance which has been progressive during six or seven years, her face growing thinner and thinner Her shoulders, upper arms, chest and trunk have also become thinner, whereas her hips and legs have become fatter These changes have been slowly but gradually progressing, as far as she and her mother can recall, for the past six or seven years

Family History—The father, aged 43, is healthy, not nervous One paternal uncle is very nervous Her mother, aged 39, is healthy, and very nervous The patient has two brothers aged 9 and 12 years, and one sister aged 14 The brother aged 9, has epileptiform seizures of recent occurrence The other brother and sister are healthy There is no history of tuberculosis, cancer or chronic disease

Past History—The patient is the oldest child in the family Her birth was normal Following the birth of this child, the mother developed septicemia and was very ill, and this child was artificially fed, had gastric disturbances until the milk was properly modified She teethed and walked at the normal time At the age of 4 years the child had adenoids removed, at the age of 8, had scarlet fever accompanied by discharge from both ears Between the eighth and ninth year she was operated on, having tonsils and adenoids removed At the age of 9 years she first attended school At the age of 10 years, she had whooping cough and at the age of 12 had measles There is no history of trauma Habits of living and diet are especially good

Menstrual History—Menstruation started at the age of 11, is regular, formerly painless, but lately there is some pain connected with the function

Present Illness—Between the eighth and ninth years the mother first noticed that the child's face and neck were thin, for which she gave her a tonic, and as she did not improve, she was taken to a physician who advised a special diet This was carried out for about one year Despite this, the wasting of the face continued Gradually this wasting was noticed in the shoulders, arms, chest, back and abdomen At the same time it was observed that the hips, thighs and legs were large and plump There are absolutely no other complaints The patient is athletically inclined and popular with her companions Her appetite is good She is happy, more or less constantly busy,

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7 Hollander, Eugen Munchen med Wchnschr, 1910, **57,** 1794

has no aches or complaints, sleeps well, and if it were not for the appearance of her face, would be perfectly contented

Physical Examination—Height, May 13, 1917, 4 feet 11¾ inches, weight, 90 pounds without clothes

Measurements—Biceps, right, 8 inches, left, 8¾ inches, forearm, right, 9 inches, left 8¾ inches, wrist, right, 6 inches, left, 6¼ inches, thigh, right, 19⅜ inches, left, 19⅛ inches, calf, right, 12⅝ inches, left, 12⅝ inches, ankle, right, 7⅝ inches, left, 7⅝ inches, chest over mammary glands, 28⅜ inches, chest below mammary glands, 26 inches, waist, 23 inches, around crest of ilium, 23⅜ inches, over anterior-superior spine, 26¼ inches, buttocks (greatest dimension), 33⅜ inches

The patient's face presents the appearance of a very emaciated, middle-aged woman, without being wrinkled The eyes are sunken, cheeks and temple fossae hollow, neck thin, with muscles standing forth prominently When she smiles deep folds form around the angles of the mouth running upward toward the zygomas On palpating a fold of the skin in her cheek one is immediately impressed with its extreme thinness The facial appearance is almost cadaverous

The chest walls show well marked intercostal spaces The shoulders are angular, with bony prominences on the clavicles, and the scapulae well defined The spinous processes of the vertebral bodies extend prominently forth The breasts are slightly pendulous and somewhat nodular The axillary and pubic hair is well defined

Below the iliac crests, the patient presents a quite different appearance The buttocks are large and covered with a thick layer of fat, the thighs are large, well rounded with the development of much subcutaneous fat The knees are dimpled and the calves of the legs large

The skin is soft, elastic and of normal color, except on the face, where it appears paler than normal There are no scars, indurations, etc The skeleton is normally developed Roentgen-ray examination of the skull, spine and upper extremities reveals no abnormalities The joints are everywhere freely movable

The head is well formed, ears set well, eyes set far back in the orbits The tongue is clean, protruded in the midline The patient has several teeth in bad condition, but this has been of very recent occurrence—within the past six months

Chest—Examination of the heart and lungs reveals absolutely nothing pathologic Examination of the abdomen is negative, with the exception of a slight increase in the liver dulness, which extends one inch below the costal margin The splenic dulness is also slightly increased

Roentgenographic and fluoroscopic examination of the stomach shows it to be of the fish-hook type, prolapsed below the crest of the ilium in the upright position The stomach, at the time of the examination, was actively contracting, emptying itself in three hours, the hepatic flexure of the colon is prolapsed, the first portion of the transverse colon being persistently fixed in the cecal region There is a marked twenty-four-hour stasis There is gastroptosis and enteroptosis (Dr Walton, roentgenographer)

Eye, Ear, Nose and Throat Examination—There is slight retraction of both eyelids Convergence is normal, eye motions are normal, extra-ocular structures are normal The pupils are active and equal The fundi and fields are normal Vision, right, 15/9, left, 15/9 Both eyes are emmetropic

The nasal examination was negative

Both ear drums are normal Hearing for the tuning fork is normal Large piece of tonsil tissue on the left side, and a fairly large sized mass on the right side (Dr William Tarrun)

Urine Single specimen, specific gravity 1 011 It is light yellow, clear, acid, with a faint trace of albumin Sugar and blood are negative Microscopically there are many epithelial cells, with an occasional white blood cell There are no casts or red blood cells A twenty-four hour specimen comprised

470 c c Specific gravity, 1 014, urea, 9 75 gm , chlorids, 5 gm Otherwise negative

Blood May 9, 1917 The Wassermann blood test was negative, hemoglobin, 90 per cent , leukocytes, 8,000, red blood cells, 4,320,000 Polymorphonuclears, 54 per cent , small lymphocytes, 25 per cent , large lymphocytes, 15 per cent , eosinophils, 2 per cent , large mononuclears, 3 per cent , transitionals, 1 per cent

Sputum None obtained

Stomach contents A double test meal given at 7 and 11 a m and drawn at 12 shows much undigested material, especially egg yolk and starch granules Free hydrochloric acid, 24 degrees, total acidity, 68 degrees, blood and bile negative

Stool Clay colored Bile and blood are absent There is an abundance of free fat present Otherwise negative

Renal function Phenolsulphonephthalein, first hour, 151 c c, 69 per cent , second hour, 40 c c, 9 per cent

Blood Pressure Systolic, 105, diastolic, 55

Sugar Tolerance May 12, 1917, 150 gm given without appearance in the urine May 13, 1917, 200 gm given without appearance in the urine

Pelvic Examination Special examination was not made

Neurologic Examination Motor function, muscle power, tone and volume are normal

Owing to the fact that this young woman is athletically inclined, there is remarkably good development and strength of her muscles The muscles in the upper extremities, shoulders and neck all stand forth prominently There are no abnormal movements, electrical reactions are normal Coordination of the upper and lower extremities, normal

Reflexes All tendon reflexes are slightly increased The superficial reflexes are all about normal The Babinski reflex is absent

Sensory Functions There is absolutely no disturbance of sensation in any of its qualities The stereognostic sense is normal

Vasomotor System Nothing abnormal was noted

Trophic Function There is marked absence of subcutaneous fat in the face, neck, shoulders, arms, chest, abdomen and back, also a marked increase in the subcutaneous fat in the buttocks, thighs, calves and legs

The organic reflexes are normal

Mental Examination—This shows an exceptionally intelligent young girl, who is quick and alert but somewhat emotional, inclined to be moody and rather sensitive She sleeps rather lightly and is easily disturbed during the night

CONCLUSION

The various diseases which might occasion wasting and those diseases in which atrophy of the bone, muscle, etc , occur were taken into consideration and in the absence of physical signs and symptoms they were excluded and a diagnosis of lipodystrophia progressiva was arrived at

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THE EFFECT OF VARIOUS NEUTRAL SOLUTIONS ON GASTRIC DISCHARGE, GASTRIC SECRETION AND DUODENAL REGURGITATION *

W E MORSE, A B, M D
CHICAGO

In a recent publication[1] attention was called to various conflicting experimental and clinical observations concerning the relation of acidity of gastric contents to the rate of gastric discharge In general, physiologic literature supports the theory that an acid reaction is essential to and hastens gastric discharge up to an optimum acidity of from 0 15 to 0 25 per cent Some clinical observers find that so-called hyperacidity increases gastric motility, while others consider it a contributing factor in stasis and gastric dilatation Motility is often unimpaired in cases of achylia gastrica Our investigations showed (1) that water is discharged from the fasting stomach of anesthetized pithed dogs more rapidly than any percentage of acid, (2) the rate of discharge is decreased with increase of acidity, (3) duodenal regurgitation as evidenced by increase in the contents of the stomach often occurred at 0 2 per cent acidity, and in nearly all trials occurred at or before 0 3 per cent acidity was reached, (4) increase in acidity augments the frequency and amount of regurgitation from the duodenum Similarly, Spencer, Meyer, Rehfuss and Hawk[2] observed that 1 0 per cent sodium bicarbonate solution hastened the discharge from the normal human stomach, while 5 0 per cent solution delayed it

Considering these various observations, Dr Hoskins suggested the possibility that the mechanism of gastric discharge might respond to stimulation by other substances than acid, that is, the control of the pylorus might be merely a nonspecific phase of the so-called "law of the gastro-intestinal tract," with a local reversal of direction at the pyloric segment when stimulation on the gastric side is supranormal If this theory were true it would follow that stimulating solutions other than acid, in low concentration, should hasten discharge from the stomach, while high concentrations would produce a regurgitation from the duodenum into the stomach

To test this hypothesis and to secure data concerning the effect of varying chemical conditions in the stomach on gastric secretion and

* Submitted for publication July 10, 1917
* From the Laboratory of Physiology of the Northwestern University Medical School

1 Morse, W E Am Jour Physiol, 1916, **41**, 439
2 Spencer, Meyer, Rehfuss and Hawk Am Jour Physiol, 1916, **39**, 462

duodenal regurgitation, several series of experiments were undertaken, using different concentrations of neutral solutions

The conditions imposed were identical with those of the acid series previously reported,[1] namely, first, a normal fasting stomach, second, fluid injections of constant temperature and quantity, but of varying concentrations, third, abolishment of inhibitory reflexes by pithing the spinal cord or sectioning the splanchnic nerve, and fourth, general ether anesthesia As a check on the foregoing, parallel experiments were made on animals with the pylorus ligated in order to eliminate any errors in the calculation of the rate of discharge from the stomach which might arise from the secretion of an unknown quantity of gastric juice

TECHNIC

There was no change in method from that used in the series of experiments previously reported[1] Ether anesthesia was maintained by the tracheal cannula-ether bottle method Through a laminectomy incision the spinal cord was destroyed from the sixth to the tenth dorsal segments, or the splanchnic nerves were sectioned above the diaphragm by opening the thorax laterally between the ninth and tenth ribs, while maintaining respiration by a Gesell apparatus Fluids were injected into and withdrawn from the stomach by means of a glass tube inserted through an esophageal fistula, opening just above the sternum Injections were made at intervals of one half hour and the amount of discharge or of regurgitation was computed by noting the difference between the amount of fluid injected and the amount withdrawn The animals were not fed during the twenty-four hours preceding the operation, and in every case the efficiency of the aspirating technic was tested by a preliminary gastric lavage, and by a postmortem examination of the gastric contents In all cases the solutions injected were titrated, before injection and after aspiration, with phenolphthalein as indicator, to determine the change of acidity during the thirty minute intervals the fluids remained in the stomach

Seven series of experiments were completed consisting of two sodium chlorid, two sodium acetate, one tabasco pepper sauce, one repeated water injection, and an extension of experiments, previously referred to, with hydrochloric acid injections into the stomach after ligation of the pylorus

Sodium Chlorid Solutions—The concentrations of solutions used varied from 0 to 10 per cent, and injections were made at thirty minute intervals In Series 1 eight animals were used The cord was pithed in the first six, in the last two the splanchnics were cut In Series 2 six animals were used and the pylorus was ligated This series was made as a check on Series 1 to determine the amount of absorption of fluids from the stomach, of secretion of fluids into the stomach, or of accumulation of fluid from osmosis, since these factors, if unknown, would render unreliable any computation as to rate of discharge from the stomach, or regurgitation of fluids from the duodenum The inhibitory mechanism was not blocked in Series 2, for it was observed in the series of continuous water injections (Table 6) that secretion as determined by acid titration was not materially altered by section of the splanchnic nerves

The results from injection of sodium chlorid solutions into the stomach are shown in Tables 1 and 2 The rate of discharge as shown in Table 1 apparently is decreased with increase of the concentration of the solution When we consider the increase in the gastric contents with the various solutions, however, when the pylorus is ligated, as shown in Table 2, we find there is more increase for the same solutions with the pylorus closed Thus

TABLE 1—DISCHARGE AND SECRETION WITH SOLUTIONS OF SODIUM CHLORID

Dog No	H_2O			NaCl 1%			NaCl 3%			NaCl 5%			NaCl 7%			NaCl 10%			H_2O		
	D	I	HCl	D	I	HCl	D	I	HCl	D	I	HCl	D	I	HCl	D	I	HCl	D	I	HCl
1†	20	0	4 0	30	0	2 0	10 0	0	2 0	0	0	2 0	50*	0	2 0	0	0	2 5	0	0	2 0
2†	12	0	3 0	5	0	2 0	0	5 0	2 0	0	15 0	2 5	0	20 0	2 5	0	10 0	2 5	8	0	1 0
3†	5	0	1 0	5	0	1 0	2 0	0	1 5	0	10 0	1 5	0	5 0	1 5	0	15 0	2 0	0	0	2 0
4†	5	0	1 0	5	0	1 0	0	5 0	1 0	0	0	1 0	0	0	1 0	0	25 0	1 0	0	0	§
5†	10	0	2 0	0	10 0	1 0	0	20 0	2 0	0	10 0	1 5	0	30 0	2 0	0	30 0	2 0	0	10	1 0
6†	5	0	1 5	0	0	1 5	0	0	1 0	0	15 0	1 0	0	15 0	1 0	0	5 0	1 0	0	5	1 0
7‡	15	0	1 2	5	0	1 4	15 0	0	1 4	0	40 0	1 5	0	20 0	1 5	0	15 0	1 5	§	§	§
8‡	6	0	1 4	8	0	1 5	8 0	0	1 7	5	0	1 6	0	7 0	1 2	0	15 0	1 4	0	0	1 4
Average	9 7	0	1 9	7 2	1 25	1 4	4 4	3 75	1 57	0 6	11 25	1 58	0	12 1	1 58	0	14 4	1 7	1	2	1 4

D = decrease of fluids in the stomach
I = increase of fluids in the stomach
HCl = hydrochloric acid expressed in terms of tenth-normal acidity per 100 c c of fluid aspirated
* = unusual occurrence not included in the average
§ = not determined
† = cord pithed
‡ = splanchnic cut

TABLE 2—SECRETION WITH SODIUM CHLORID SOLUTIONS PYLORUS LIGATED

Dog No	H_2O			NaCl 1%			NaCl 3%			NaCl 5%			NaCl 7%			NaCl 10%		
	A	I	HCl	A	I	HCl	A	I	HCl	A	I	HCl	A	I	HCl	A	I	HCl
1	0	0	2 0	2 0	0	2 0	0	0	1 5	0	15 0	1 0	0	20 0	2 0	0	18 0	2 0
2	6 0	0	1 0	0 0	4 0	1 0	0	0	1 2	0	18 0	1 0	0	14 0	1 6	0	16 0	1 2
3	0	0	1 0	0 0	0	0 6	0	10	0 6	0	15 0	1 0	0	23 0	1 2	0	65 0	1 8
4	5 0	0	1 7	4 0	0	1 0	0	0	1 0	0	20 0	1 2	0	35 0	1 2	0	18 0	1 6
5	5 0	0	1 0	8 0	0	1 0	0	5	1 0	0	0	1 0	0	45 0	1 2	0	30 0	1 5
6	10 0	0	1 2	5 0	0	1 2	0	15	1 2	0	35 0	1 7	0	35 0	1 9	0	35 0	2 2
Av	4 3	0	1 31	3 1	0 66	1 13	0	5	1 1	0	17 1	1 15	0	28 66	1 5	0	30 0	1 7

A = absorption
I = increase of fluids in the stomach
HCl = hydrochloric acid expressed in terms of tenth normal acidity per 100 c c of fluid

for 5 per cent solutions, with the pylorus open we have an average increase of 11 25 c c, while with the pylorus ligated the increase is 17 1 c c, leaving an excess of 6 15 c c which represents discharge Also the excess with the pylorus ligated over the amount of increase with patent pylorus, is 16 55 c c for 7 per cent solutions and 15 9 c c for 10 per cent solutions This indicates an increase rather than a decrease in the rate of discharge

The increase in the contents of the stomach with high concentrations of sodium chlorid solutions both with the pylorus closed and with it open is supposedly due largely to osmosis Secretion, however, contributes a small part to the aggregate amount This is shown by the fact that the total acidity remained fairly constant with both open and closed pylorus, hence the secretion of acid was not accelerated by the presence of the solution or increase in concentration The amount of acid secreted in the thirty minute intervals varied from 1 4 to 1 7 c c tenth-normal acidity per 100 c c Taking the average increase in acidity as 1 58 c c of tenth-normal hydrochloric acid per 100 c c, this would give 3 18 c c of tenth-normal acid for the total 200 c c of fluid aspirated Considering the acidity of the gastric juice as 0 5 per cent, as demonstrated by Heidenhain,[3] Pawlow,[4] Sommerfeld,[5] Carlson,[6] and others, this would give an equivalent of 2 7 c c of gastric juice It is therefore evident that the contribution of secretion to the increase of fluid is small

Regurgitation also is excluded by the fact that the increase was greater when the pylorus was closed than when open Presence of bile was never observed, but the amount of mucus increased with increase in concentration

Some individual variations are noted, the most pronounced of which is found in Animal 1, Table 1, which showed rather larger discharge than usual, these were associated with liquid bowel movements and at necropsy the gastric mucosa was hemorrhagic The large discharge obtained in the case with 7 per cent solution was so unusual that it was eliminated from the averages

Sodium Acetate Solutions, Series 3—Ten dogs were used in this series and in all cases the splanchnic nerves were cut The concentrations used varied from 0 to 10 per cent In the first four experiments, solutions of acetate gradually increasing to 10 per cent were employed In the last six only water and 10 per cent solution were injected, after which the pylorus was ligated and the animals transferred to Series 4 This latter is the companion series, being utilized as a check on the secretory or osmotic factors involved Seven animals were used in Series 4, of which only the first was independent of Series 3 By study of the results of the first four animals of Series 3 and the first animal of Series 4 it was surmised that the work could be expedited without materially reducing the value of the data by testing first the discharge of water and 10 per cent sodium acetate, and then after ligation of the pylorus, testing the secretion or osmosis with the same concentration of solutions on each animal Thus, Experiment 2 of Series 4 is continuous with Experiment 5 of Series 3, and the others following in consecutive order

The results are shown in Tables 3 and 4 There is a decrease in discharge with increase in concentration, as shown by the results in Table 3 There is also an increase in the fluid contents of the stomach, with increase in concentration, and the average increase is the same for 10 per cent concentration with the pylorus open and closed This would indicate that the rate of discharge is decreased from an average of 12 2 c c with water to 0 with 10 per cent acetate The amounts of increase both with the pylorus open and closed is less with acetate than with the chlorid, and the amount of mucus was less Bile was never observed The increase in acidity is fairly constant both for

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3 Heidenhain Arch f d ges Physiol, 1872, **19,** 153

4 Pawlow Work of the Digestive Glands (Trans W H Thompson), London, 1910, p 32

5 Sommerfeld Arch f Anat u Physiol, Suppl, 1905, p 455

6 Carlson Am Jour Physiol, 1915, **38,** 258

TABLE 3—DISCHARGE AND SECRETION WITH SOLUTIONS OF SODIUM ACETATE

Dog No	H_2O			Sodium Acetate 0 5%			Sodium Acetate 1%			Sodium Acetate 3%			Sodium Acetate 5%			Sodium Acetate 10%			H_2O		
	D	I	HCl	D	I	HCl	D	I	HCl	D	I	HCl	D	I	HCl	D	I	HCl	D	I	HCl
1	12 0	0	1 0	7 0	0	2 0	7 0	0	2 0	0	n	3 0	0	0	3 0	0	12 0	2 5	0	5 0	1 0
2	10 0	0	3 0	25 0	0	2 5	0	10	3 5	0	5 0	3 5	0	0	4 0	0	5 0	4 0	8	0	2 5
3	15 0	0	2 5	10 0	0	2 5	10 0	0	2 5	0	5 0	3 0	0	10 0	3 0	0	3 0	2 5	0	0	1 5
4	0	0	2 0	5 0	0	1 5	5 0	0	1 0	5 0	0	1 5	0	8 0	1 5	0	13 0	2 0	0	10 0	0 5
5	20 0	0	1 6													0	5 0	1 6			
6	0	0	2 0													0	0	1 6			
7	15 0	0	1 6													0	6 0	2 4			
8	15 0	0	1 6													0	10 0	7 7			
9	30 0	0	1 6													0	10 0	2 0			
10	5 0	0	3 6													0	5 0	4 4			
Average	12 2	0	2 05	11 75	0	2 1	5 5	2 5	2 25	1 25	2 5	2 75	0	4 5	2 88	0	6 9	3 07	2	3 8	1 88

D = decrease of fluids in the stomach
I = increase of fluids in the stomach
HCl = hydrochloric acid expressed in terms of tenth normal acidity per 100 c c of fluid
The splanchnic nerves were sectioned in all cases

TABLE 4—SECRETION WITH SOLUTIONS OF SODIUM ACETATE PYLORUS LIGATED

Dog No	H_2O			Sodium Acetate 0 5%			Sodium Acetate 1%			Sodium Acetate 3%			Sodium Acetate 5%			Sodium Acetate 10%			H_2O		
	A	I	HCl	A	I	HCl	A	I	HCl	A	I	HCl	A	I	HCl	A	I	HCl	A	I	HCl
1	2	0	1 5	5	0	1 5	5	0	2 5	0	0	2 5	0	5	2 5	0	5 0	2 5	*	*	*
2																0	0	2 0	5 0	0	2 0
3																0	12 0	2 0	0	15 0	2 0
4																0	2 0	1 6	0	11 0	2 0
5																0	5 0	2 0	0	18 0	2 4
6																0	20 0	1 2	0	20 0	1 6
7																0	0	1 6	0	0	2 0
Average																0	6 29	1 8	0 8	10 66	2 0

* = not determined
D = decrease of fluids in the stomach
I = increase of fluids in the stomach
HCl = hydrochloric acid expressed in terms of tenth normal acidity per 100 c c of fluid
The splanchnic nerves were cut in all cases

TABLE 5—Discharge and Secretion with Tabasco Pepper Sauce

Dog No	H_2O			Tabasco Pepper Sauce 15 C c to L				H_2O			Tabasco Pepper Sauce 15 C c to L		
	D	I	HCl	D	I	HCl		D	I	HCl	D	I	HC[illegible]
1	10 0	0	0 8	14 0	0	0 8		0	8 0	0 8	0	0	0 [illegible]
2	12 0	0	0 8	10 0	0	0 8		0	0	1 2	0	0	1 [illegible]
3	5 0	0	1 6	0	0	1 6		10 0	0	2 0	15 0	0	2 [illegible]
4	8 0	0	1 2	5 0	0	2 0	Pylorus Ligated	0	0	1 2	4 0	0	2 [illegible]
5	0	0	1 2	20 0	0	1 2		0	0	1 2	15 0	0	1 [illegible]
6	46 0	0	1 2	26 0	0	1 6		0	7 0	1 2	0	4 0	1 [illegible]
7	5 0	0	2 0	10 0	0	1 2		4 0	0	1 2	0	2 0	1 [illegible]
Average	12 2	0	1 25	12 1	0	1 3		2 0	2 1	1 26	4 1	0 9	1 [illegible]

D = decrease of fluids in the stomach
I = increase of fluids in the stomach
HCl = hydrochloric acid expressed in terms of tenth-normal acidity per 100 c c
In all cases the spinal cord was pithed

water and all percentages of acetate used Increase in the fluid content here also is attributed primarily to osmosis We are unable to explain the high average of 10 66 c c increase in the gastric content with injections of water after ligation of the pylorus, and after the injection of 10 per cent acetate, as shown in Table 4 It is possible that this increase is due to an exudation following irritation of the mucosa, although the mucosa at necropsy was not congested

Solution of Tabasco Pepper Sauce—Concentrations sufficient to produce a burning peppery taste were used, a result which was obtained with 15 c c of pepper sauce to the liter Seven animals were used and in all cases the spinal cord was pithed Two injections were made before and two after the ligation of the pylorus, giving the discharge and secretion rate of each animal as in Series 3 and 4 Water was first injected followed by the solution of pepper sauce When discharge had been noted, after thirty minute intervals, for each solution the pylorus was ligated and the injections repeated to obtain data concerning secretion

The results are given in Table 5 It is noted that there is practically no difference in the rate of discharge with water and with solutions of tabasco sauce Also the secretion rate and acidity are practically unchanged

Repeated Injections of Water—Water was repeatedly injected in a series of ten animals In the first five the splanchnic nerves were cut, in the last five, the inhibitory mechanism was left intact In the first two animals the injections were repeated at thirty minute intervals, in the remaining cases the interval was one hour These experiments were made to determine whether fatigue, continued narcosis or a progressive development of shock played a significant rôle in modifying the rate of discharge The results are shown in Table 6. It is seen that the average rate of discharge is unchanged at the end of three hours and but slightly reduced at the end of five hours The initial rate of discharge for each animal remains practically unchanged throughout the experiment, and the same is true for the amount of acid secreted Also, there is practically no difference in discharge or acid secretion with the splanchnic nerves cut or intact

TABLE 6—Repeated Determinations of—

Splanchnics Cut

Dog Number	H_2O ½ Hour			H_2O 1 Hour			H_2O 1½ Hours			H_2O 2 Hours		
	D	R	HCl	D	R	HCl	D	R	HCl	D	R	HCl
1	10 0	0	5 6	13 0	0	3 2	10 0	0	2 0	5 0	0	1 6
2	15 0	0	1 2	12 0	0	0 8	6 0	0	0 8	11 0	0	0 8
3				10 0	0	1 0				5 0	0	1 2
4				0	0	1 0				4 0	0	1 0
5				5 0	0	1 0				12 0	0	0 6
Splanchnics Not Cut												
6				12 0	0	1 4				18 0	0	1 8
7				7 0	0	1 2				7 0	0	1 0
8				13 0	0	1 6				9 0	0	1 2
9				5 0	0	1 8				0	2 0	1 4
10				25 0	0	1 4				5 0	0	1 8
Average	12 5	0	3 4	10 2	0	1 4	8 0	0	1 4	7 6	0 2	1 24

D = discharge from the stomach
R = regurgitation into the stomach
HCl = hydrochloric acid expressed in terms of tenth normal acidity per 100 c c

Injections of Hydrochloric Acid with the Pylorus Ligated—This series is an extension of experiments previously reported[1] It shows the effect of various concentrations of hydrochloric acid on gastric secretion The animals were pithed and the pylorus ligated The solutions varied from 0 to 0 5 per cent The results as given in Table 7 show practically no secretion with any concentration except in one unusual case with 0 5 per cent acid, in which 12 c c of secretion were obtained The acidity of the solution injected is decreased during the thirty minute interval and the neutralization is greater for the higher percentages

DISCUSSION

The solutions used in the experiments were chosen on the basis of nontoxicity, solubility and importance of the substances in dietetics or therapeutics

Attention has previously been called[1] to the small discharge of water obtained under the conditions imposed in these experiments as compared with that obtained by Moritz[7] from duodenal fistulas In the various experiments on gastric discharge performed in this laboratory a total of fifty-one dogs have been used In each animal the rate of discharge of water was ascertained as a standard for comparison with the rate for various solutions The average discharge of water from

7 Moritz Ztschr f Biol 1901 42, 584

—THE RATE OF DISCHARGE OF WATER

H_2O 2½ Hours			H_2O-30ns 3 Hours			H_2O 3½ Hours			H_2O 4 Hours			H_2O 4½ Hours			H_2O 5 Hours		
D	R	HCl	D	R	HCl	D	R	HCl	D	R	HCl	D	R	HCl	D	R	HCl
Splanchnics Cut																	
12 0	0	1 6	5 0	0	1 6	11 0	0	1 6									
20 0	0	0 8	15 0	0	0 8	10 0	0	0 8									
			13 0	0	1 4				5 0	0	1 2				14 0	0	1 1
			6 0	0	1 0				5 0	0	1 0				10 0	0	1 0
			12 0	0	0 6				0	0	0 6				10 0	0	1 0
Splanchnics Not Cut																	
			25 0	0	1 4				15 0	0	1 6						
			0	2 0	1 0				5 0	0	1 0				5 0	0	1 2
			10 0	0	1 2				25 0	0	1 2				0	0	1 2
			5 0	0	1 8				5 0	0	1 4				5 0	0	1 4
			15 0	0	1 0				0	3	1 0				15 0	0	1 2
16 0	0	1 2	10 6	0 2	1 18	10 5	0	1 2	7 5	0 4	1 1				7 4	0	1 0

these fifty-one animals was 14 3 c c in thirty minutes Of these fifty-one individuals, six had a discharge exceeding 25 c c, while five animals showed no discharge If these extreme cases are eliminated, we have forty which show within a narrow margin of deviation an average discharge of 10 c c per half hour It is hoped that future observations will determine what conditions are responsible for this relatively slow rate It is possible that general ether anesthesia or the presence of a tube in the cardiac orifice of the stomach may be significant factors As previously noted,[1] Cannon[8] determined that section of the splanchnic nerves in cats resulted in no change of the normal movements of any part of the alimentary canal, and Carlson[9] found that section of the splanchnics in dogs increased the gastric tonus and augmented gastric hunger contractions This eliminates the possibility that destruction of the inhibitory mechanism is the significant factor

Pawlow[10] found that gastric secretion is only slightly stimulated by the introduction of water into the stomach, and that solutions of meat ash, chlorid and hydrochloric acid produced the same results as water alone Throughout these experiments small but constant amounts of acid have been noted Titration for total acidity, using phenolphthalein

8 Cannon Am Jour Physiol, 1906, **17**, 431
9 Carlson Am Jour Physiol, 1913, **32**, 382
10 Pawlow Am Jour Physiol, 1913, **32**, 112

as indicator, was made after each aspiration The notations in the tables are in terms of tenth-normal acidity per 100 c c As the total gastric contents were 200 c c, this represents half of the total acid secreted in the thirty minutes that the fluid remained in the stomach By computing the amount of gastric juice from the acid present it is found that in thirty-five animals the rate of secretion per thirty minutes in the presence of water varies with few exceptions from 1 4 c c to 5 6 c c, with an average of 2 33 c c The injection of other solutions as sodium chlorid, sodium acetate and tabasco sauce does not materially change this rate The average secretion for sodium chlorid is 2 27 c c, for sodium acetate 3 3 c c, and for tabasco pepper sauce 2 c c Hydrochloric acid also produces no essential change in the rate of secretion

TABLE 7—Secretion with Solutions of Hydrochloric Acid Pylorus Ligated

Dog No	H_2O			HCl 0 1%			HCl 0 2%			HCl 0 3%			HCl 0 4%			HCl 0 5%		
	A	S	HCl	A	S	HCl	A	S	HCl	A	S	HCl	A	S	HCl	A	S	HCl
1	0	0	1 6	0	4	—3 6	0	1	—6 0	0	0	—11 6	0	0	—16 8	0	12 0*	—19 6
2	0	0	2 0	0	0	—4 0	0	0	—7 2	0	0	—10 0	0	3	—16 0	0	5 0	—16 0
3	15 0	0	2 0	0	0	—2 0	0	0	—5 6	0	0	—8 0	0	0	—6 0	0	0 0	—10 0
4	5 0	0	1 4	0	0	—2 0	5 0	0	—6 0	0	0	—10 0	0	0	—15 0	0	0 0	—17 0
5	5 0	0	1 8	0	0	—2 0	5 0	0	—2 8	5	0	—4 8	0	0	—5 2	0	5 0	—13 2
6	7 0	0	2 0	0	0	—3 2	0	0	—4 0	0	2	—6 0	0	0	—10 0	0	0 0	—12 0
Av	5 3	0	1 8	0	0 66	—2 8	1 66	0 17	—5 26	0 83	0 33	—8 4	0	0 5	—11 5	0	3 66	—14 6

* = unusual result
A = absorption from the stomach
S = secretion into the stomach
HCl = hydrochloric acid expressed in terms of tenth normal acidity per 100 c c of fluid
Minus sign indicates decrease in acidity

The cord was pithed in all cases

as shown by the data in Table 7 Here, with the pylorus ligated, the average increase in the gastric contents varies from 0 with water to 3 66 c c with 0 5 per cent hydrochloric acid The high average obtained with 0 5 per cent hydrochloric acid solution is largely due to one unusual result of 12 c c increase With all other percentages of acid used the average increase was less than 1 c c These findings are corroborative of the observations of Pawlow [10]

Carlson[11] observed that the gastric glands of the human stomach are never quiescent, but continue to secrete from 2 c c to 50 c c per hour The results obtained in these experiments show the rate of secretion for the dog's stomach under the conditions specified approximates the minimum for the human stomach in the nonactive state

11 Carlson Am Jour Physiol, 1915, 37, 50

Rehfuss and Hawk[12] have presented direct evidence of the secretion of gastric juice of constant acid concentration by the human stomach In our experiments, continued presence of a fairly constant amount of acid in the total gastric contents, as determined at thirty minute intervals, also indicates that the rate of secretion of acid is constant for a given stimulus

The data obtained from injection of hydrochloric acid solution into the stomach after ligation of the pylorus are shown in Table 7 This series is an extension of experiments[1] referred to as evidence that secretion is not a disturbing factor in computing the rate of gastric discharge with acid solutions In addition to the evidence they afford as to the amount of secretion in the presence of hydrochloric acid solutions, the observations indicate that there is probably a neutralizing substance in the gastric secretions which increases with increased acid concentration in the stomach contents With 0 1 per cent hydrochloric acid there is a decrease in the acidity of the solution which varies from 2 to 4 c c of tenth-normal acidity per 100 c c, with an average of 2 8 c c This decrease is larger for each higher acid concentration until an average neutralization of 14 6 is reached with 0 5 per cent hydrochloric acid As the titrations were made for total acidity with phenolphthalein indicator, this decreased acidity cannot be attributed to combination of the acid with mucus Slight hemorrhage into the stomach was frequently present, but by color comparison with a solution of known hemoglobin content it was estimated that these hemorrhages would not exceed 2 c c, which could not account for the amount of the progressive increase in the extent of the neutralization No tests were made for the presence of ammonia, hence it cannot be asserted that this was the factor producing the decrease in acidity, but since ammonia has been demonstrated in the gastric contents by numerous investigators, as tabulated by Huber,[13] and in the pure gastric juice by Strauss[14] and Carlson,[15] it must be considered a factor in the neutralization of the acid, and in the absence of other demonstrable sources of neutralization it is probably the principal factor Huber[16] finds that the amount of ammonia has no relation to the concentration of acid or pepsin As previously noted in our experiments, the amount of neutralization is proportional to the concentration of the acid However, the ether anesthetic might be a factor in stimulating the liberation of ammonia which Huber[17] finds to have a complex origin, repre-

12 Rehfuss and Hawk Gastro-Intestinal Studies, Jour Am Med Assn, 1914, **63**, 2088
13 Huber Am Jour Physiol, 1917, **42**, 405
14 Strauss Berl klin Wchnschr, 1893, **30**, 398
15 Carlson Am Jour Physiol, 1915, **38**, 248
16 Huber Am Jour Physiol, 1915, **38**, 418
17 Huber Am Jour Physiol, 1915, **38**, 419

senting excretion from the blood, deamidization in the gastric mucosa, or possibly the action of gastric flora In our experiments the gastric flora is eliminated as a possible factor by the acid concentration of the solutions used, the limited time interval and the frequent lavage produced by repeated aspirations

The possibility has also to be considered that the decrease in acidity might have been due, not to neutralization, but to resorption of the acid

SUMMARY

1 Solutions of sodium chlorid varying from 1 to 10 per cent slightly augment the rate of discharge of fluids from the stomach of anesthetized and pithed or splanchnicotomized dogs Solutions of concentration above 3 per cent produced an increase of fluid in the stomach by osmosis, but with the pylorus ligated the increase exceeded that obtained with the pylorus patent, sufficient to indicate a discharge greater than the discharge with water

2 Solutions of sodium acetate slightly retard the discharge of fluid from the stomach of anesthetized and splanchnicotomized dogs

3 The fluid content of the stomach is usually increased when solutions of sodium chlorid or sodium acetate are injected in concentration above 3 per cent This increase is attributed to osmosis exceeding the amount of discharge

4 The rate of secretion of gastric juice as computed from the increase of acidity averages 2 33 c c per thirty minutes, when water is injected into the stomach and the pylorus is patent This rate of secretion is not materially altered by ligation of the pylorus or injection of solutions of sodium chlorid, sodium acetate or tabasco pepper sauce

5 The acidity of solutions of hydrochloric acid injected into the stomach of anesthetized dogs with pylorus ligated is decreased, the rate of diminution increasing with increase in the acidity of the solutions

6 The average discharge of water from the stomach was 14 3 c c per thirty minutes in fifty-one trials By eliminating eleven extreme cases the average for forty animals is reduced to 10 c c

7 Solutions of tabasco pepper sauce are discharged from the stomach at practically the same rate as water

8 The mechanism of gastric discharge does not react to solutions of sodium chlorid, sodium acetate and tabasco pepper sauce, in the same manner that it reacts to solutions of hydrochloric acid

I wish to express my gratitude for the many helpful suggestions given by Dr R G Hoskins in connection with this work

A SIMPLE TECHNIC FOR THE DEMONSTRATION OF A PHAGOCYTIC MONONUCLEAR CELL IN PERIPHERAL BLOOD

FIRST REPORT OF STUDIES ON THE MONONUCLEAR CELLS OF THE BLOOD *

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The purpose of this report is to describe a method by which a mononuclear cell constantly present in normal blood may be shown to be phagocytic, and to point out certain characters of the cell that suggest its origin

The origin, morphology and many of the functional activities of the polymorphonuclear leukocytes (neutrophilic, eosinophilic and basophilic) of the blood are known, but considerable uncertainty exists in regard to the mononuclear group of leukocytes While it seems quite certain that lymphoblastic cells constitute a large part of the mononuclear leukocytes, the classification of the remaining mononuclear cells that are present is not satisfactory An important aid in tracing the origin of cells in sections of tissue is their relationship to the surrounding ones that divide to form them, but the leukocytes in the blood stream do not arise there by mitosis, and once they are swept away in the blood their position in regard to the other cells near them is no longer of value in tracing their origin In face of the uncertainty concerning the mononuclear blood cells, terms such as transitional leukocyte, and large mononuclear leukocyte, that are not histologic terms imply a definite embryologic origin, have been commonly used

Attempts at the identification and classification of nonlymphocytic mononuclear leukocytes have for the most part been based on staining characteristics Methods dependent on the functional activities of the blood cells have, however, been employed, and of these vital staining has attracted most attention The usual statement of observers employing this method is that cells which stain vitally do not appear in the peripheral blood, or they appear there in negligible numbers

TECHNIC EMPLOYED

The method used is simple, but some of the details require considerable care in their execution The object to be attained is to bring

* Submitted for publication Sept 26, 1917
* From the Pathological Laboratory of the Boston City Hospital

the leukocytes into contact with fine particles of carbon at the body temperature and under exact and uniform conditions, and then to fix and stain them properly

Three cubic centimeters of blood are added to 2 c c of 3 8 per cent sterile sodium citrate that contains 1 per cent by weight of a good commercial grade of lampblack The citrate-lampblack liquid is shaken vigorously in the flask to secure as even a suspension as possible, and 2 c c immediately placed in a 15-c c graduated centrifuge tube to which the blood is added at once To obtain the blood the palmar surface of a finger tip is painted with tincture of iodin, wiped with 95 per cent alcohol, dried, punctured deeply with an automatic lance and the blood pressed out so that the drops fall directly into the tube The citrated blood is mixed thoroughly by striking the lower end of the centrifuge tube with the finger and immediately is filtered through a single layer of muslin that has been laundered into a second centrifuge tube in order to remove the gross particles of lampblack The second tube may be prepared by autoclaving it with the cloth pressed into its upper portion in the form of a cone The cloth is moistened with a 3 8 per cent citrate solution before the citrated blood is poured on it It is not advisable to filter the suspension of lampblack before mixing with the blood because it tends to filter clear

The filtered citrated blood is placed in a centrifuge and whirled at a moderate speed for fifteen minutes and at a high speed for five minutes The tube is removed from the centrifuge and the black leukocytic layer on the surface of the corpuscles is carefully drawn with suction into a large bore hemocytometer pipet Such a pipet may be kept in 80 per cent alcohol and washed with sterile citrate before filling The pipet is shaken for one minute, a wide rubber band stretched over it to close the ends, and then transferred to an incubator at 37 5 C where it is kept in a horizontal position for one hour, being removed and shaken for one minute at the end of fifteen, thirty and forty-five minutes

At the end of the hour the pipet is taken from the incubator, shaken for five minutes and coverglass preparations made in the usual way, the small drops of blood being placed on the coverglasses from the pipet Slides are not suitable

To stain the coverglass smear, 2 drops of a polychrome blood stain are placed on it for one minute At the end of one minute four drops of distilled water are added and the diluted stain allowed to remain on it for two to three minutes The stain is washed off with water, differentiated for ten seconds in 0 02 per cent yellowish water-soluble eosin, washed with water, dried and mounted in colophonium-xylol

Any polychrome blood stain that has a reaction properly adjusted may be used The writer's blood stain obtained from Bausch and Lomb Optical Co, Rochester, N Y, was employed in making most of the stains If a number of preparations are to be stained the coverglasses are supported on the tops of small test tubes 12 mm in diameter held in a test-tube rack, and the center of each pressed on with a 1-mm glass rod while the alcoholic stain is spread out with a second rod A single preparation may of course be held in suitable coverglass forceps

The results and conclusions as recorded below are based on the preparations made by the foregoing technic Since it would clearly be an advantage to employ a more direct method in the examination of pathologic blood, many variations of the test have been tried, but even slight variations have usually yielded negative results It has not been possible to eliminate the centrifugation, but the undiluted blood

may be employed for making the smears, and this appears to be the simplest and most accurate way for the differential counting of leukocytes In employing undiluted blood the ingestion of the carbon by the leukocytes is found to be determined by the concentration of the citrate In the stained film there is no difficulty in distinguishing mononuclear cells containing carbon from polymorphonuclear ones that contain it, but the best picture is obtained if phagocytosis by the neutrophils is prevented To do this 7 7 mg of sodium citrate per c c of blood are used This amount of citrate does not interfere with the phagocytic properties of the mononuclear cells, but 15 mg prevent ingestion by all leukocytes If only 5 mg of citrate are used more than half of the neutrophils as well as the phagocytic mononuclear cells ingest the carbon

To use the undiluted blood four small glass beads and 8 mg of a dry lampblack-citrate powder are placed in a small test tube 45 mm long prepared from glass tubing with an inside diameter of 7 mm, and 1 c c of water added The tube is shaken and the upper surface of the liquid marked by scratching with a file The liquid is washed out, the tube dried, the beads replaced, another 8 mg of lampblack-citrate powder added and blood dropped into it from the finger until the upper surface reaches the mark The finger is pricked with an automatic lance and the drops of blood allowed to touch the apex of a small wire in the shape of the inverted letter V inserted into the upper end of the tube This prevents the blood from coming into contact with the mouth of the tube The tube is stoppered with a rubber cork, vigorously shaken for five minutes, centrifuged at a moderate rate of speed for fifteen minutes and placed in the incubator for one-half hour at 37 5 C, care being taken not to disturb the leukocytic layer The tube is removed from the incubator, shaken for two minutes, centrifuged, again incubated for one half hour, shaken for two minutes after removal from the incubator and coverglass preparations made and stained The red and white hemocytometer pipet may be filled from the undiluted blood before the first incubation for the enumeration of the white cells and erythrocytes The second shaking, centrifugation and incubation are required to bring all the leukocytes into contact with the carbon The small drop of blood is placed on the coverglass by means of a capillary pipet with nipple attached The films are allowed to dry in the air for at least three hours before the stain is applied

The preparation of the lampblack-citrate powder is important It is prepared by mixing intimately 7 7 gm sodium citrate (Merck), U S P, of highest purity, that has been ground to small granules in a mill (not powdered in a mortar) with 0 3 gm lampblack that has been ground in a mortar for thirty minutes The powder is placed in a bottle and kept in a desiccator

RESULTS OBTAINED

On examination of the smears with an oil-immersion lens the general picture is seen to resemble that obtained with any good polychrome stain A striking difference, however, is observed in certain of the mononuclear cells the cytoplasm of which contains many carbon particles or is completely filled with the lampblack, while the lymphocytes and the great majority of the polymorphonuclear cells contain none, and those that do contain it have taken up a much smaller amount than

the phagocytic ones of the mononuclear group The smears are surprisingly free from extracellular carbon deposited on the red blood corpuscles and in the plasma Since not a single cell that is a lymphocyte of the small variety contains the particles, the phagocytic mononuclear cells as a result of the carbon they contain are readily distinguished If it were not for the carbon within these cells, however, some of them would be mistaken for large lymphocytes, although most of them would fall in the classes commonly known as transitional and large mononuclear leukocytes

The morphologic characters of the mononuclear phagocytic cell, aside from the ingested carbon, are well defined within certain limits, and most of the cells can be identified in the usual blood smear after the study of lampblack preparations, but all of them cannot be recognized with certainty The average diameter of the cell closely approximates that of the polymorphonuclear neutrophil, but the individual cells present greater variations Many are smaller than the neutrophils and approach the larger lymphocytes in size, while a few are larger than any neutrophil The cell outline is usually round, but irregularities may be produced when the smear is made, or pseudopodia may be present as the result of ameboid activity

The cytoplasm of this class of cells filled with the carbon particles is characteristic Much lampblack is taken up by all cells of this variety, and many of them contain so great an amount that the character of the cytoplasm cannot be distinguished

The zone of the cytoplasm is wide at some point, due to an indentation or eccentric position of the nucleus, and in preparations stained in the usual way this is, perhaps, next to its phagocytic properties, the most distinguishing feature of the cell The cytoplasm is often present only in sufficient amount to form a distinct band about the nucleus, but it may be fully as wide as the nucleus itself In those cells in which the cytoplasm is distinct it is seen to stain less blue than that of the lymphocytes It may be quite free of granules, but usually there are present granules that are much like the neutrophilic granules, except that they are more filament-like The filamentous granules color like those of the neutrophils by the oxydase reaction, but are usually less distinct Typical discrete "azur" granules, such as occur so commonly in lymphocytes, have not been observed

The nucleus is round or oval, is horseshoe or saddle-back in shape, or presents a broken irregular contour Rarely a cell of this type is encountered in which the nucleus is stellate or divided into separate chromatin masses Cells with this morphology appear to be formed during the hour of incubation, but it is not certain that an occasional cell of this class with a broken nucleus does not occur in the blood The only important characteristic of the nucleus is that it is very rarely

both regular in outline and centrally placed It stains less heavily than the nucleus of the neutrophils

The number of this variety of cells in the blood of five normal individuals varies from 5 6 to 8 1 per cent, with an average of 7 2 per cent In obtaining these percentages above 2,000 cells were counted in each sample and the direct method used, since it is not certain that the percentages in leukocytic layers after centrifugation are the same as in the whole blood The average number of other cells is as follows lymphocytes, 32 2 per cent, neutrophils, 58 5 per cent, eosinophils, 1 6 per cent, basophils, 0 5 per cent The average number of leukocytes present per c mm is 6,820 The coverglass preparations were mounted in pairs on slides and the cells counted from at least three such pairs with the use of a mechanical stage

DISCUSSION AND CONCLUSIONS

The functional behavior of fixed tissue cells is constantly made use of in their identification, and of the cell functions phagocytosis is one that is important and has attracted a great deal of attention In general the phagocytic properties of the cells commonly met with are known Fibroblasts, identified by the use of appropriate stains, rarely or never are found to have incorporated foreign particles within their cytoplasm; none of the enormous number of lymphoblastic cells found in various normal and pathologic tissues are phagocytic, while polymorphonuclear neutrophils incorporate different bacteria and may ingest nonbacterial substances

In the lesions of typhoid fever, in tubercles and in other pathologic processes endothelial cells divide, become free and migrate through the vessel wall into the extravascular tissue This is seen in single oil-immersion fields of tissue that is perfectly preserved These free mononuclear leukocytes of endothelial origin are frequently phagocytic for other tissue cells, red blood corpuscles, certain bacteria and for various nonbacterial particles such as carbon The mononuclear cells of the blood shown by these experiments to be phagocytic for carbon correspond in morphology and phagocytic properties to the endothelial leukocytes of the tissues, and it seems likely that this class of leukocytes may prove to be of endothelial origin That they are not related to the polymorphonuclear leukocytes is clearly shown by their phagocytic properties

In order to determine the behavior of tissue cells during life, certain coal tar and natural dyes have been injected into animals intravenously and by other routes, and the tissues examined after a varying number of hours and days Vitally stained cells are said not to be present in the peripheral blood of the animals treated in this way, but granules

of the stain are present in tissue cells spoken of as macrophages, which is a term implying that the cells containing the granules are capable of phagocytosis The term phagocytosis is not correctly applied to the passage of a substance in solution into the protoplasm of a living cell, although it is there changed over into insoluble granules It is not possible to say whether all phagocytic cells are vitally staining or not, but certainly intravital staining as commonly carried out is useless for the demonstration of phagocytic cells in the blood

In designating the mononuclear cells of the blood that are phagocytic by the above method as a separate and distinct variety of leukocyte, factors other than the morphology of the cells are taken into account Although the cells in the preceding experiments remain in the incubator for one hour only, they retain their ameboid activity and staining properties for four days at 37 5 C, and there is no reason to think that the behavior of the cells toward carbon particles under optimum conditions in vitro is in any way an abnormal manifestation That all cells have an opportunity to ingest by phagocytosis the carbon and yet that none but this variety do ingest it is shown by the presence of the large amount ingested and its absence from other cells except a few of the polymorphonuclear neutrophils

Since none of the small mononuclear cells that are typical lymphocytes ingest the carbon, it is evident that lymphocytes and phagocytic mononuclear cells are comprised in the mononuclear group of leukocytes It is believed that all of the phagocytic cells, owing to their resemblance to large lymphocytes especially, cannot be accurately identified by means of any of the blood stains now in common use without the employment of a reaction to determine their phagocytic properties

[The writer gratefully acknowledges his obligation to Dr F B Mallory for the privilege of carrying on this work in his laboratory and his indebtedness to Mr L Massopust for the illustration which accompanies this paper]

Description of Plate

Drawn with camera lucida and oil-immersion lens from a single cover-glass preparation

A, group consisting of neutrophil, erythrocyte and mononuclear cell containing carbon, outline of nucleus of phagocytic cell is a broken curve

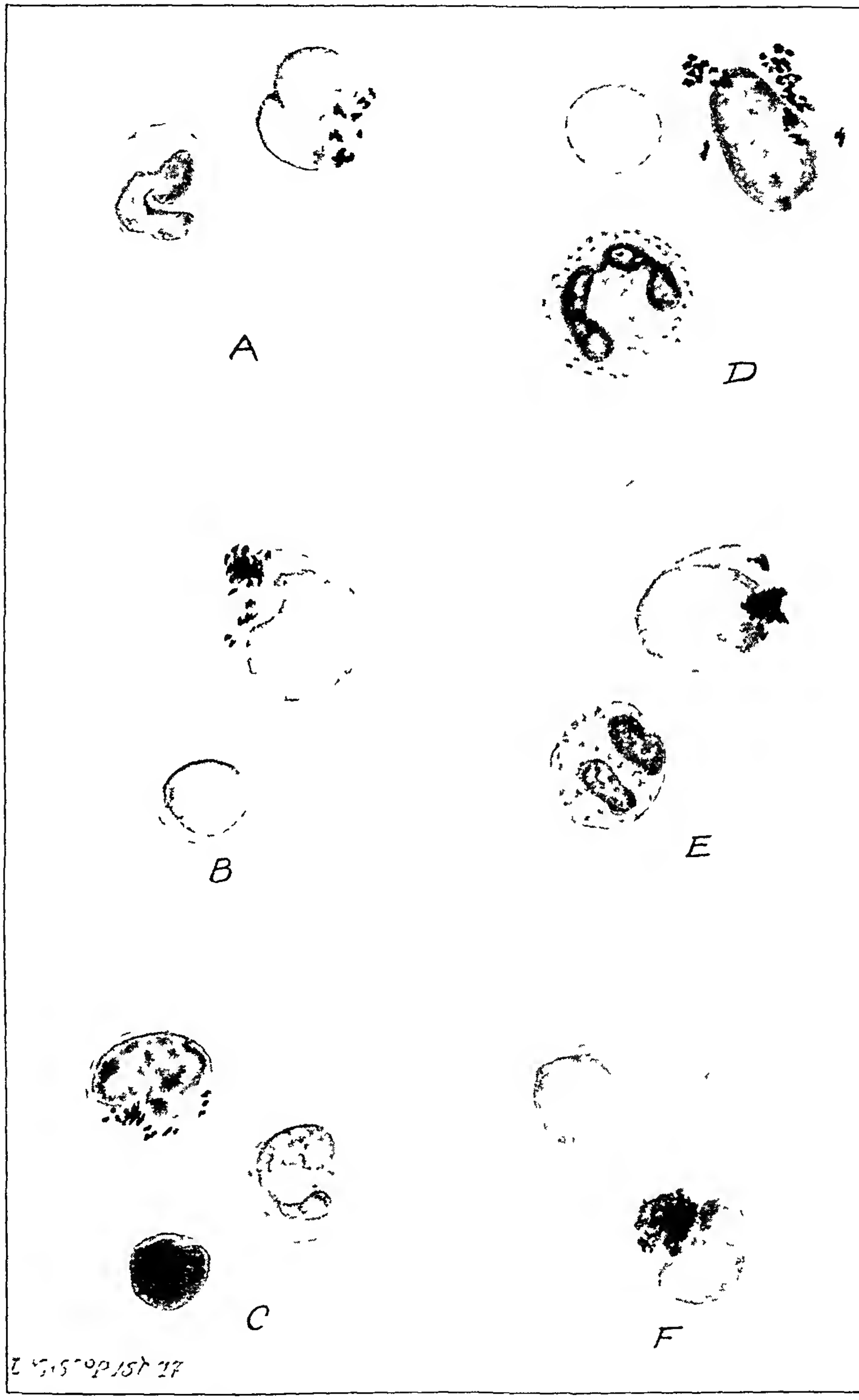
B, lymphocyte, erythrocyte and phagocytic cell with an irregular nucleus

C, lymphocyte, neutrophil and phagocytic cell with saddleback nucleus

D, neutrophil, erythrocyte and phagocytic cell Note that all elements in this part of the coverglass smear are large The nucleus of the carbon-containing cell is oval

E, erythrocyte, neutrophil and phagocytic cell with oval nucleus

F, erythrocyte, lymphocyte and phagocytic mononuclear The phagocytic cell resembles the lymphocyte morphologically


A
D
B
E
C
F

in whom a pineal shadow was demonstrated by roentgen-ray examination Timme[5] recently published a series of cases of progressive muscular dystrophy Five of these patients were examined roentgenologically and four of them, who were above the age of puberty, showed shadows in the pineal region The youngest patient, 14 years of age, failed to show any shadow As the patients were quite young and symptoms of their disease had begun in childhood, it is possible that in these cases the pineal gland was diseased and so lent itself more readily to the process of calcification, or more probably, involution of the gland may have occurred earlier than normal, with consequent exaggeration of the deposit of brain sand

In our case the calcification of the pineal is an evidence of the degenerative processes of senescence, which are manifested as well by the extreme arteriosclerosis and calcification elsewhere in the body It is not astonishing that there were no symptoms referable to the pineal gland Whatever function the pineal gland may have is exercised before puberty The pineal secretion is supposed to inhibit growth With pineal disease this inhibition is removed and there is adiposity, general bodily overgrowth, with precocious sexual development, increase in size and development of the sex organs, and precocious change of voice in boys After puberty the pineal gland undergoes involution, and so one would not expect symptoms from pineal calcification after adolescence

CONCLUSIONS

Shadows due to calcification in the pineal gland are found quite frequently in roentgenograms of the skull In the vast majority of cases the calcification is only an exaggeration of the deposit of brain sand found normally in the pineal gland of adults As would be expected, these shadows are found more frequently with advancing age Since the calcification occurs in the course of the normal involution of the pineal gland, it has no significance except in very young individuals In these it may be an evidence of an abnormally early involution of the pineal gland, which, if it occurs at the period when the gland is normally physiologically active, may cause symptoms due to insufficiency of the pineal secretion

5 Timme, W Progressive Muscular Dystrophy as an Endocrine Disease, The Archives Int Med, 1917, **19,** 79

ANATOMIC OBSERVATIONS CONCERNING THE MECHANISM OF BILE RESORPTION IN JAUNDICE *

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The manner in which bile is resorbed from the liver into the blood, general circulation and tissues presents much that is still unclear and uncertain

The subject is complicated by our imperfect knowledge of the finer structure of the liver For, while the direct relation of the liver cells to blood and bile capillaries is not quite definitely settled, there exists no agreement whatever as to the presence or absence of lymph channels in the acini It is held by some that perivascular lymph sheaths lie between liver cells and capillaries,[1] while others positively deny this [2]

The question, then, as to whether bile resorption in the liver occurs as the result of primary lymph or direct blood resorption, is complicated by anatomic uncertainty

The physiologic experiment is unable to solve this problem, for not only are the observations and conclusions of experimenters quite contradictory,[3] but lymph and blood have naturally been collected for analysis outside of the liver, sometimes at considerable distance, where a relation to the primary channels of resorption cannot with certainty be determined, and in which modifications by collateral circulation, secondary diffusion and other possible influences on bile contents of lymph and blood, cannot be satisfactorily estimated

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* Submitted for publication July 21, 1917

* From the pathological laboratories of the Royal Victoria Hospital and of McGill University

1 Disse Arch f. mikr Anat, 1890, **36.** Burker Pfluger's Arch f Ges Physiol, 1901, **83,** 241 Eppinger, Jr Ziegler's Beitr z path Anat u z allg Path, 1902, **31,** 230 Kretz Ergebn d allg Path u path Anat, 1904, **2,** 502 Ibid, Handb d allg Path, v Marchand and Krehl, 1913, **2,** Part 2, p 468 Reinke Verhandl d anat Gesellsch, 1898, No 12

2 Schafer Textbook of Microscopic Anatomy Longmans, Green Co, 1912, p 571 Herring and Simpson Proc Roy Soc Med and Surg, 1906, **78.** Browicz Bull Acad d Sc de Cracovie, July, 1899, January and May, 1900 Teichmann Abhandl d k preuss Akad d Wissensch Krakau 1899, **34.** Kaufmann Spec Path Anat, Berlin, Georg Reimer, 1911, **1,** 565

3 Kaufmann Spec Path Anat, Berlin, Georg Reimer, 1911, **1,** 637 Kretz Ergebn d Path u path Anat, 1904, **2,** 502, Ibid, Handb d allg Path, v Marchand and Krehl, 1913, **2,** Part 2, p 468 Whipple and King Jour Exper Med, 1911, **13,** 115

If the immediate path of bile resorption remains undecided, it is generally conceded that the mediate cause lies in bile obstruction in, or outside of, the liver by either coarse mechanical means or finer intrahepatic impediments to the bile flow cholangeitis, pericholangeitis, bile thrombi or a thick, so-called pleiomorphous bile

I

The conditions consequent on the first cause, that is, coarse mechanical occlusion of the larger bile ducts, are perhaps best understood and commonly summarized under the term obstructive jaundice The classic example of obstructive jaundice is stone in the common duct, which may either obliterate the duct entirely, or, at least, narrow it to such an extent as to bring about dilatation and backward pressure into all other bile ducts, which gradually extend into the bile capillaries Bile consequently stagnates, ultimately bile capillaries rupture, and finally bile imbibition with necrosis of the liver cells results

This well known, common picture may be variously modified and complicated by accompanying infections and inflammatory changes Very similar, of course, are the results from obliterations or partial obstructions of the hepatic duct

During the later stages of obstructive icterus certain changes occur in the contents of the larger bile vessels, the most conspicuous of which is gradual resorption of bile pigment and substitution of the bile by a thick or thin mucoid, viscid fluid, so that the bile canals appear finally as cystic dilatations

As simple and easy of comprehension as this course of events seems on first sight, and as it has been fixed in our mind by experience, there still remain some links in this chain which need strengthening, especially in the light of some unusual but very notable and positive exceptions to the rule

A particularly impressive exception which, in a way, carries the weight of an experiment, came recently to necropsy in these laboratories It illustrates, quite apart from its theoretical importance, that a considerable, if not complete, obstruction of the common bile duct and hepatic ducts may occur, sufficient to produce ecstasy even in their smaller branches in the liver, without any general or even local hepatic jaundice and, apparently, even without subjective symptoms

As far as can be determined, the case differs in extent and manner of obstruction from those mentioned in literature unfortunately only in a casual way without the care which they deserve

Thus, Rolleston[4] says

4 Rolleston Diseases of the Liver Macmillan, 1912, p 749 Griffon Bull Soc anat, Paris, 1896, **71**, 513 (Quoted by Rolleston)

Jaundice which has been marked early in the course of impaction, may wane and finally disappear, and after death a loose calculus may be found in the duct Griffon records four cases of this kind in which the calculus was found just above the biliary papilla In exceptional instances there may never at any time be jaundice, although the common duct contains calculi

Unfortunately, no mention is made of the size of these calculi, their exact position, physical constitution and stability or mobility, and whether they lead in the cases referred to, to obstruction, back pressure and dilatation of the ducts This is, of course, the all important matter in the production of jaundice

Kaufmann[5] also refers to such instances in a cursory way He writes, in reference to obstructions of the common duct "In rare cases a tremendous stone may occur (as author saw, over thumbthick) without jaundice" But he gives no further details Aschoff[6] makes no mention of such cases Ziegler[7] also makes no reference to these exceptions

REPORT OF CASE

History—The case observed in these laboratories concerns a man 73 years of age who was admitted to the Royal Victoria Hospital July 12, 1916, and who died July 17, 1916

He complained of inability to pass urine, and of constipation for the previous three months For two weeks before admission catheterization had been employed He had lost considerable weight, was rather poorly nourished, but showed no other abnormal physical signs and gave no history of other symptoms

Family history and personal history were negative, and he gave no account of any previous illness

Examination—Examination disclosed a smooth, but irregular, hypertrophied prostate The urine contained some blood and pus cells

Operation—July 13, under local anesthesia, the first stage of a prostatectomy by suprapubic incision, with drainage, was performed

July 15 the patient's general condition was much worse, pulse became weak and irregular and he died July 17, at 9 30 p m

Necropsy—Necropsy (117'16) showed the body of a man of about the age stated, 175 cm in length, of good frame, but of poor nutrition, skin pale and clear, with a number of ecchymotic spots on the right shoulder and axilla, pupils were unequal, conjunctivae clear

Section disclosed no free fluid in the abdominal cavity, several loops of small intestine in the lower left quadrant were dark greenish in color and there were numerous recent fibrinous adhesions between different loops of bowel and parietal peritoneum in the region of the descending colon Outside of an enlarged prostate, no other essential lesions were found except the following unsuspected condition of the liver and bile ducts While still in situ a very marked dilatation of the extrahepatic bile ducts was noticeable The gallbladder, on palpation, revealed a large number of stones, but some thin bile could be squeezed with difficulty from the gallbladder into the duodenum

On palpation of the thick common duct a large calculus was found, located, practically impacted, at the ampulla of Vater (Fig 1) On opening the common duct this gallstone was oblong, egg-shaped, and measured 3 by 1 5 cm

5 Kaufmann Spec Path Anat, Berlin, Georg Reimer, 1911, **1**, 631
6 Aschoff Path Anat, II, Jena, Gustav Fisher, 1913, p 914
7 Ziegler Spec path Anat, Jena, Gustav Fischer, 1902, p 651

The duct itself measured at the papilla 3 cm in diameter Following the duct upward, it was found to contain three other large, irregular, cherrystone-sized, as well as a number of smaller, pea-sized stones, six in number It was markedly dilated throughout, its widest portion, about 5 5 cm above the papilla, measured 4 cm in diameter At the junction of the cystic and hepatic ducts the diameter was also 4 cm

The much dilated main hepatic duct contained one large, firmly lodged calculus rather irregularly triangular in shape and the size of a large cherrystone Above it were seven smaller, pea-sized, loose stones varying somewhat in size This duct measured 2 25 cm in diameter

The right branch of the main hepatic duct contained four large pea-sized stones and a number of other seedlike concretions It measured 1 cm in diameter

The left branch of the main hepatic duct contained a large pea-sized stone and also a number of seedlike concretions Its diameter was 1 5 cm

The intralobar ducts were visibly dilated and measured from 2 to 4 cm in diameter Many contained fine granular bile precipitations Smaller, pointlike, greenish discolored ducts were also to be seen in the liver substance, the parenchyma, however, was not jaundiced, but rather pale, reddish brown, with indistinct markings, and generally intact and firm

Fig 1—Photograph of gallstones found in case of obstruction of bile ducts without icterus 1 Stones contained in common duct, *a* Large stone impacted at ampulla 2 Stones in gallbladder 3 Stones in main hepatic duct 4 Stones in hepatic duct of left lobe in liver 5 Stones in hepatic duct of right lobe in liver (For further description see text)

The dilated bile ducts did not show any thickening of their walls, but were stained a bright green But this discoloration extended nowhere into the surrounding liver substance

The cystic duct measured 0 5 cm at its origin

The gallbladder was distended, contained some yellowish bile and a large number, about twenty, of variously sized and irregularly shaped stones

The consistency of all stones was very firm, hard, with rounded, smooth but strong edges

Analysis showed the calculi to be largely cholesterin precipitated around an organic nucleus, with a considerable amount of bile pigment

Microscopic Examination—Microscopic examination of the liver showed parenchyma and interlobular tissue intact There was nowhere dilatation, bile engorgement or inflammation of the interlobular bile ducts, and the columnar arrangement of the liver cells within the acini was not disturbed The acinar blood capillaries were somewhat engorged, especially around central veins, but bile precipitation or engorgement of bile capillaries was entirely lacking and liver cells appeared uniformly healthy

We are dealing, therefore, in this instance with an apparently marked obstruction of the large intrahepatic and extrahepatic bile ducts, which, however, has not extended into the smaller interlobular ducts and acinar bile capillaries

The question arises how to explain this, more especially, how to account for absence of bile stasis in the parenchyma and lack of icterus

There can be no question that the obstruction was severe, if not complete All anatomic evidence points in that direction the location, size, consistency and number of stones as well as the tremendous, sausage-like dilatation of the ducts themselves Whether the obstruction was ever an absolute one is of course not possible to answer with certainty, for we possess no record of the color of feces during life, and the necropsy protocol does not specify any abnormality in them However, this is not, it seems to me, of essential importance, for admitting some bile to have escaped, which is indeed quite possible, it is certain that the obstruction was sufficient to cause ecstasy of the bile ducts It remains, then, to be answered why this did not extend to and include the interlobular ducts and intra-acinar bile capillaries and liver cells Every pathologic anatomist will recall cases of severe obstructive jaundice in which the obstruction appeared less complete and the dilatation of the ducts less pronounced than here, and still was considered sufficient to account for the occurrence of icterus It follows, therefore, that additional factors enter into its formation besides the mere mechanical blocking of the ducts One of these is well known, and I shall simply mention it in passing, for it does not directly concern this issue, namely, inflammation of the bile ducts An even moderate stasis may, by secondary ascending cholangeitis and pericholangeitis, lead to severe jaundice But such cases are not of pure stasis, unlike the case here before us, and they stand, therefore, outside of this discussion

One other point must be settled at the start, namely, whether this case belongs to the rare category, mentioned by Rolleston, in which fading of pigmentation, almost to disappearance, occurs Judging from the meager records, this appears to follow a reestablishment of bile flow in which, therefore, the obstruction, say from one stone, was relieved by mobilizing it That is not comparable to this case at all Moreover, the entire integrity of the liver cells, the general preservation of their architecture, the lack of necroses or evidences of regeneration as seen after necroses, together with the perfectly normal appearance and arrangement of interlobular structures, make a previous jaundice most improbable, for such a complete, uniform recovery from what must have been a severe and lasting icterus to absolutely normal conditions in a case in which, as we know, the obstruction has not been relieved, seems to me impossible The explanation must, therefore, be sought elsewhere

Now it is well known that a resorption of bile in the liver occurs only with the existence of considerable over-pressure Burker has shown that this follows an overpressure of 20 mm Hg The place of resorption is in the portal zone of the liver parenchyma, not from the interlobular ducts lined by cylindrical epithelium It is evident, therefore, that the pressure in the parenchyma can never have risen here sufficiently to force the bile back into, or interfere with the discharge of bile from, the bile canaliculi and interlobular ducts This much seems certain, but just how and why this was avoided can, with our present knowledge, only be surmised

In the first place, much may depend on the manner and rapidity with which obstruction occurs When an obstruction takes place slowly and gradually (not unlikely in this case by entire absence of subjective history or symptoms) the results are apt to be very different from rapid occlusion with normal bile flow For it is conceivable that when the bile stagnation in the larger ducts has gradually reached a certain degree, diminution or even cessation of bile formation may occur (Reflex action?) The pressure of the bile may, therefore, never become great enough, especially if some slight outflow is intermittently possible, to extend to the interlobular bile ducts and to the acinar canaliculi, although a sufficient bile volume may gradually accumulate in the larger and extrahepatic ducts to cause them to dilate [8]

The character of the bile itself must also be of importance For a thin, watery bile would not only be less apt to exert overpressure, but would, by virtue of its easy flow, be more apt to escape by the obstructing agent into the duodenum and thus just counterbalance a rise of pressure through the interlobular ducts into the bile capillaries A thick, slowly flowing, viscid bile would naturally have opposite effects

I consider, therefore, that rapidity and manner of obstruction, together with the character of the bile, are most probably of fundamental importance in the results of interference with the bile flow through the large extrahepatic ducts, thus, even severe obstruction may be regulated by a gradual adaptation to the new conditions and the creation, so to speak, of a new mechanism of bile elimination

I might in this connection refer here briefly to another case, recently under observation, of a woman, 48 years of age, dead from hemorrhage after hysterectomy and cholecystotomy for gallstones Necropsy (50 17) disclosed two small, loose stones in the hepatic duct 2 cm above the junction with the common duct Above this point the larger branches of the hepatic duct showed moderate dilatation There was no general jaundice The liver weighed 1,600 gm, was pale mottled,

8 Experiments with regard to these points are at present conducted in our laboratories

yellowish and very friable, fatty, with indistinct markings Microscopically, the liver showed patchy, irregular bile precipitation in limited areas around the central veins in swollen, fatty, vacuolated liver cells with much blood stasis, but no general icterus, no diffuse bile imbibition of liver cells or bile in the acinar canaliculi The lobular periphery, particularly, was everywhere free from bile Evidently this patchy, limited, central bile retention in liver cells was in this instance not due to extrahepatic obstruction at all, and was probably attributable to other causes namely, severe venous congestion with subsequent changes in the liver cells

It would be instructive to obtain in similar rare or unusual cases detailed information and analysis regarding the points here discussed and thus gain a more exact knowledge of the conditions underlying icterus consequent on pure obstruction of common or hepatic duct than we command at present

II

If we have seen that the conditions leading to jaundice in pure obstruction are not as simple as they appear at first sight, they become much more complicated in those cases in which no gross obstruction may be discovered, that is, in the various forms of so-called hematogenous, toxemic or hematic icterus That the liver is essential for its production is now generally conceded, although the observations of Whipple and Hooper[9] seem to indicate that bile may be formed on intravenous injection of hemoglobin into dogs after exclusion of the liver from the circulation, and the investigations of Joannavics[10] point to the necessity of the spleen as a preparator of blood corpuscles for the production of bile by the liver Its exact mechanism is, however, not definitely known Most generally accepted are the ideas of Stadelmann,[11] Minkowski,[12] and the more definite views of Eppinger, Jr, according to which an excessive production of a pleiochromous, thick bile occurs (hypercholia) which cannot be normally discharged, and therefore enters the blood (parapedesis) Eppinger, Jr,[13] has furnished a more definite anatomic conception by demonstrating bile thrombi (intracapillary bile thrombosis) in the liver of these cases According to these views, the hematogenous jaundice is, in the last instance, an intra-acinar obstructive jaundice

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9 Whipple and Hooper Jour Exper Med, 1913, **17**, 593 and 612

10 Joannavics Ztschr f Heilk, Path Abt, 1904, **25**, 25, Ibid, Recherches experimentales sur la pathogenese de l'icters Prize essay Brusseles, 1903

11 Stadelmann Der Icterus, Stuttgart, 1891

12 Minkowski Kongress f inn Med, 1894, Ibid, Ergebn d Path u path Anat, 1897, **2.**

13 Eppinger, Jr Ziegler's Beitr z path Anat u z allg Path, 1902, **31,** 230, and 1903, **33,** 123

It is particularly in this connection that the question of bile absorption by lymph or blood stream has been actively discussed Eppinger, Jr, Kretz and others firmly believe in the existence of intra-acinar lymph channels, while again others (notably anatomists and histologists) deny their existence entirely The views of Eppinger, Jr, and Kretz are largely based on pathologic evidence In edematous livers and those in which loss or shrinkage of liver cells occurs, there appear definite perivascular sheaths between capillaries and liver cells, occasionally filled with amorphous coagulum These are regarded by them as perivascular lymph spaces or roots of lymphatics I have convinced myself of their existence in a number of livers

The stain which I have long employed for these and other sections in which exact definition, differentiation and contrast are desired consists in deeply staining paraffin sections in hematoxylin (long washing with few drops of concentrated solution of lithium carbonate added to the wash water), immersion in a concentrated solution of picric acid, with almost immediate withdrawal and thorough washing in abundance of water

Counterstain with a solution of watery eosin, prepared by adding drop by drop a strong solution of eosin to a large test tube of water until the color of the water is bright red, for about thirty to forty-five seconds Wash thoroughly in water, rapidly dehydrate clear in oil of bergamot, mount (It is well to control each step under low power of the microscope) Protoplasm stains purplish, nuclei deep blue, red cells yellow, fibrous tissue pink Cell and nuclear outlines and definitions, reticulum, and contrasts come out exceedingly well by this method It is more delicate than Van Gieson's stain, and well adapted for microphotographic purposes In suitable cases the perivascular spaces are definite and plain according to this method But I am conscious that it is difficult to exclude artefacts, that is, an artificial separation of capillaries from the cells Nevertheless, it must be admitted that their general and uniform appearance in cerain cases argues against that view, as well as observations in jaundiced livers to which I shall refer later

To return to the consideration of the mechanism by which toxic or hematic icterus is produced The observations and views of Minkowski,[12] Stadelmann[11] and Eppinger, Jr,[13] which are strongly supported by Kretz, furnish a satisfactory explanation for a number of these cases, but by no means for all For there are others in which neither a thick, pleomorphous bile nor bile thrombi can be demonstrated Every pathologic anatomist recalls cases of hematogenous icterus in which these are absent It is, therefore, necessary to account for them in some other way

It has been suggested that bile thrombi, the original cause of the icterus, have disappeared,[11] this is a view I cannot share, for the whole histologic picture in many of these cases is quite different from those due to pleomorphous bile and bile thrombi Instead of coarse, plump precipitations and coagulations in intercellular canaliculi and liver cells, these cases show a fine, diffuse, granular bile precipitation in the protoplasm of the liver cells, usually with cell swelling and patchy cell

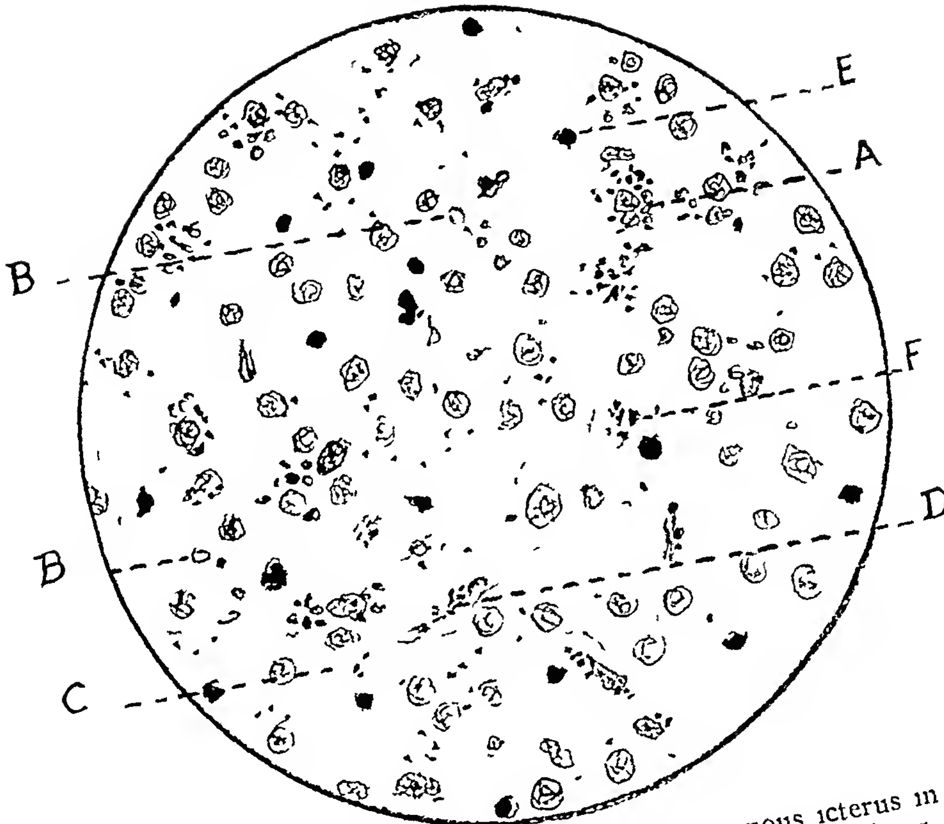

Fig 2—Microscopic section from liver in hematogenous icterus in pernicious vomiting of pregnancy (Zeiss Object 4 mm D D Ocular 8) *a* Liver cells containing diffuse granular and clumpy bile pigment, partly in process of solution *b* Fading and bile forming red blood cells within liver cells *c* Perivascular space with bile pigment passing into capillary *d* Lining endothelial cell of capillary containing bile pigment *e* Leukocyte with bile pigment *f* Capillary lumen with free granular bile pigment (Hematoxylin-picric acid-eosin stain)

loss It has been suggested by Sterling[14] that jaundice may result from injury to liver cells, which leads to disorganizations or occlusion of the smallest intracellular bile canals by swelling or fibrin plugs But the great objection to this explanation is the fact that relatively few cases of parenchymatous degeneration or edema in the liver are associated with bile retention and resorption, and that even quite general and extensive necroses may occur without the slightest evidence of jaundice or even local bile precipitation I have only recently examined the liver from a patient with fatal septicemia consequent to gangrene of the gut in a strangulated hernia, which showed very prettily all stages of pure toxic liver necroses, but there was nowhere any evidence of icterus

The same is true of chronic venous congestion in which, as I[15] have pointed out elsewhere, severe jaundice may occur, particularly toward the end of the process On the other hand, jaundice may be absent even in quite extensive necroses in venous cyanosis, or at least may lead only to slight icteric tinge of conjunctivae with very little evidence of bile precipitation and resorption in the liver itself Plainly, therefore, parenchymatous swelling, cell loss, even extensive necroses are in themselves not sufficient to account for jaundice Something else is also essential

Some light may be thrown on this question by observations I have recently made in a number of cases of hematogenous jaundice to which the views of Stadelmann and Eppinger, Jr, seemed not applicable They were cases of sepsis, pneumonia, and toxic lesions of pregnancy accompanied by definite general icterus It has already been said that these cases presented a characteristic histologic picture Bile was rather diffusely "dusted" or "sprinkled," mostly in fine granules, spherules and minute clumps throughout the liver sections Closer inspection showed it precipitated within turbid protoplasm of degenerating and fading liver cells These precipitations did not correspond to intracellular casts of fine canaliculi On the contrary, none of these could be discovered Higher magnification showed further characteristic pictures, which were especially well displayed in the liver of a woman dead with marked jaundice from toxic vomiting in pregnancy (Fig 2) (Necropsy 25, '17) Here it was seen that the fine, granular pigment was gradually set free from the liver cells, possibly washed away, but frequently by direct fading and loss of cells It was then to be observed in the perivascular sheaths, as already described by

14 Sterling Arch f exper Path, 1911, **64.**

15 Oertel, H The Archives Int Med, 1910, **6,** 293, Ibid, Berl klin Wchnschr, 1912, **41,** 2019, Ibid, Bull Johns Hopkins Hosp, 1917, **28,** 318

Mallory,[16] and also in the lining endothelial cells of the capillaries, Kupfer's cells, and, furthermore, in the capillaries themselves, where it appeared partly in leukocytes and partly free in granules and minute clumps I have observed in the same case pictures resembling somewhat those described by Rossler[17] as phagocytosis of red blood cells by liver cells In some of the liver cells could be noted fading yellowish disks, evidently red blood cells, some of the bile spherules in the same cells so closely approached in size and outline red blood cells that they suggested a direct local transformation of hemoglobin into precipitated bile, a view further strengthened by some pictures suggesting stages of that process

On the other hand, in a recent case of severe typhoid fever in which there was no evidence of icterus, the liver cells, which were enormously, acutely swollen, turbid and very edematous, showed phagocytosis of red cells and blood pigment, with rapid fusion and fading of the hemoglobin, but no precipitation Evidently the pigment went rapidly into solution within the watery cell protoplasm

It would appear, therefore, that this icterus depends primarily not on blocking of the finer ducts, but lack of entrance, that is, proper discharge of bile into the bile canaliculi

Many years ago (1893) Liebermeister,[18] from purely theoretical considerations, advanced the view that hematogenous icterus resulted from inability of the liver cells to retain the bile which, therefore, diffused into blood and lymph He spoke of this as akathectic icterus (from the ακάθεκτος of Plutarch)

These theoretical conceptions were, of course, rather vague, and have, for this reason, never enjoyed much favor, nevertheless, they are to some extent borne out by these investigations

He was right when he traced the ultimate cause of hematogenous icterus to the liver cells themselves For our observations indicate that the lack of proper discharge of bile into the finest canaliculi is due to an alteration in cell protoplasm which throws the bile out of, respectively prevents its entrance into, the cell emulsion

What, then, is the cause of this bile precipitation?

It may be due to a ferment, and, indeed, Gideon Wells,[19] based on the work of Lang,[20] is inclined to take this view as to the manner of

16 Mallory Principles of Pathologic Histology Philadelphia, Saunders Co, 1914 p 117

17 Rossle Ziegler's Beitr z path Anat u z allg Path, 1907, **41,** 181

18 Liebermeister Deutsch med Wchnschr, 1893, **19,** 365

19 Wells, G Chemical Pathology, Philadelphia, Saunders Co, 1914, p 443 (footnote)

20 Lang: Ztschr f exper Path u Therap, 1906, **3,** 473 (Quoted by Wells) Lang has demonstrated the presence of fibrinogen in the bile of phosphorus poisoning

formation for the bile thrombi observed by Eppinger, Jr But it is perhaps justifiable to assume, from our present knowledge of the internal structure of protoplasm and in harmony with the morphologic findings described above, that this fine, diffuse bile precipitation depends on specific changes in the colloidal state of the cells by certain toxic substances This would explain why some infections and intoxications are more apt to lead to icterus than others

Swelling, degeneration and disorganization of the cells are associated with and follow these changes, but it is clear that in themselves they are unable to produce icterus as long as bile is kept in protoplasmic solution, or perhaps better, emulsion

If bile precipitation is the first requisite for the production of jaundice, the second requisite is, as has been shown, discharge of the pigment, either through cell (protoplasmic) currents, or, especially, through cell disintegration and loss, into the perivascular spaces and passage of the bile into the blood capillaries

The conclusion is reached, therefore, that bile resorption in hematogenous icterus may occur by intra-acinar lymph and blood resorption almost simultaneously

I am aware of the fragmentary character of these contributions, but incomplete as they are, they emphasize the importance and desirability of renewed, especially anatomic and histologic, observations in obstructive as well as toxic icterus

STUDIES ON THE METABOLISM IN GOUT *†

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Gout is generally considered a disease of metabolism For this reason different types of metabolic studies have been made by a large numbers of investigators A summary of these investigations will be found in the reports of Magnus Levy,[1] McClure and Pratt[2] and McClure[3] The gaseous metabolism of gouty patients was studied by Magnus Levy by means of the Zuntz method of indirect calorimetry He found the heat production calculated on the basis of body weight and the respiratory quotients to be within the limits of variation considered as normal We have made a study of the heat production of gouty persons as calculated from the oxygen consumption for the three following reasons

1 In order to compare the heat production during the period of acute gouty attacks with that present when the patients were free from symptoms

2 For the purpose of comparing the basal metabolism of gouty patients on purin-free and nuclein-rich diets

3 To be able to calculate the total heat production of gouty persons according to the linear formula of Du Bois[4]

EXPERIMENTAL PROCEDURE

Only those patients were selected for study who possessed tophi from which sodium urate crystals were obtained After patients were on a purin-free diet from four to twenty-three days their metabolism and the total nonprotein nitrogen in the blood were determined Then daily additions of 150 gm of cooked sweetbreads were made to their otherwise purin-free diet over a period of two to five days At the end of this time the basal metabolism and blood nonprotein nitrogen were again estimated

Basal metabolism was determined by the indirect method of calorimetry The usual mask covering the nose and mouth was used and the expired air was collected in a Tissot spirometer Analyses for oxygen and carbon dioxid

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† From the Medical Service of the Peter Bent Brigham Hospital

1 Magnus-Levy, A Ueber Gicht Klinische Beobachtung, chemische Blutuntersuchungen und Stoffwechselversuche Ztschr f klin Med, 1899, **36,** 353

2 McClure, C W, and Pratt, J H Uric Acid in Gout The Archives Int Med, 1917, **20,** 481

3 McClure, C W The Renal Function in Gout The Archives Int Med, to be published

4 Gephart, F C, and DuBois, E F The Basal Metabolism of Normal Adults with Special Reference to Surface Area The Archives Int Med, 1916, **17,** 902

were made with the Haldane gas analysis apparatus Subjects were kept at complete rest in bed without food or drink for eight hours before running an experiment Each experiment consisted of two to three periods of about ten minutes each in which the expired air was collected The results of these periods will be given in tables with the report of the different cases Total nonprotein nitrogen in the blood was determined by the direct nesslerization method of Folin and Denis[5] Uric acid in the urine was estimated by Folin's modification of the method published in his laboratory manual[6] The modification consisted in substituting the "uric acid reagent" for the "uric acid and phenol reagent"

The basal metabolism has been studied in one gouty patient receiving a mixed diet, in one during an acute attack, and in three, first on a purin-free, and then on a nuclein-rich diet At the time of the metabolism experiments the latter three patients were free from gouty symptoms

SYNOPSIS OF CASE REPORTS

CASE 1—M W S Med No 6264 White, male, aged 40 Admitted to the Peter Bent Brigham Hospital March 10, 1917, and discharged April 25, 1917

Diagnosis Chronic nephritis, hypertension, acute uremia, gout, question of a patent ductus arteriosus

The patient habitually drank two bottles of beer daily For the previous twenty-five years he had had attacks of acute arthritis which were characterized by the symptoms usually ascribed to gout In recent years the attacks had been polyarticular and from one to seven weeks in duration The last attack began in the right wrist two days before entering the hospital March 9, 1917, the patient developed uremic coma

Physical examination March 10, 1917 The patient was a well nourished man lying in a stuporous condition A small tophus was present in each ear from which sodium urate crystals were obtained The area of cardiac dulness measured 13 cm to the left in the fifth interspace, and 4 cm to the right in the fourth interspace A loud, rough systolic murmur was audible over the precordium and of maximum intensity along the left sternal margin and in the pulmonic area The heart's action was regular The walls of the radial arteries were barely palpable Blood pressure was 200 mm systolic and 100 mm diastolic There was some swelling of the right hand and wrist

The urine contained a heavy trace of albumin, many casts, and a few erythrocytes The blood carbon dioxid was 30 6 mm The blood contained 49 mg of urea nitrogen per 100 c c and the McLean[7] index of urea excretion was 11 5 per cent The phenolsulphonephthalein excretion was 21 per cent in two hours

By March 12, 1917, the patient had recovered from his attack of uremia and of gout On a purin-free diet the amount of blood urea nitrogen fell gradually to 27 mg per 100 c c on April 4, 1917 The index of urea excretion remained low but the phenolsulphonephthalein excretion for two hours rose to 40 per cent

CASE 2—W P G Med No 6625 Negro, male, aged 43 Entered the Peter Bent Brigham Hospital May 16 and was discharged May 28, 1917 Diagnosis Gout, very questionable chronic nephritis

The patient's habits were good During the previous ten years he had had a dozen attacks of gout affecting the joints of the lower extremities and of the phalanges of the fingers On physical examination numerous tophi were found in the ears and about the finger joints Otherwise, physical examination was

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5 Folin, O, and Denis, W Nitrogen Determinations by Direct Nesslerization II Nonprotein Nitrogen in Blood Jour Biol Chem, 1916, **26**, 491

6 Folin, O A Laboratory Manual of Biological Chemistry New York, 1916

7 McLean F C, and Selling Lawrence Urea and Total Nonprotein Nitrogen in Normal Human Blood Relation of Their Concentration to Rate of Elimination Jour Biol Chem, 1914, **19**, 31

TABLE 1—Basal Metabolism of Gouty—

Case	Date	Experiment No	Period	No Days of Purin Free Diet Prior to Experiment	Height in Cm	Weight in Kg	Surface Area in Sq M	Rectal Temperature	Duration of Experiment Period in Min	CO_2 Production
1	4/ 1/17	1	I	23	170 5	54 8	1 64	97 8	10 05	2 97
			II						10 00	2 96
			Average							2 97
2	5/25/17	2	I	7	177 5	65 4	1 82	98 2	10 03	3 63
			II						10 05	3 67
			Average							3 65
3	4/ 2/17	3	I	11	163 0	90 6	1 98	99 6	9 98	3 29
			II						10 00	3 36
			III						10 00	3 29
			Average							3 31
	7/ 2/17	4	I	3	163 0	91 2	1 96	99 0	9 98	3 13
			II						9 97	3 16
			Average							3 15

* Basal metabolism calculated according to the linear formula of DuBois

TABLE 2—Basal Metabolism of Gouty—

Case	Date	Experiment No	Period	No Days of Purin Free Diet Prior to Experiment	Height in Cm	Weight in Kg	Surface Area in Sq M	Rectal Temperature	Duration of Experiment Period in Min	CO_2 Production
1	4/ 6/17	1	I	2	170 5	55 0	1 64	98 0	9 97	3 17
			II						10 10	3 16
			III						10 03	3 07
			Average							3 13
2	5/27/17	2	I	3	177 5	65 6	1 82	98 0	10 02	3 44
			II						10 03	3 43
			Average							3 44
3	4/ 9/17	3	I	5	163 0	90 6	1 98	98 0	10 03	3 22
			II						10 03	3 39
			Average							3 31
	7/ 5/17	4	I	3	163 0	92 4	1 98	98 4	9 90	3 38
			II						9 97	3 37
			Average							3 38

* Basal metabolism calculated according to the linear formula of DuBois

—Patients Receiving a Purin-Free Diet

O_2 Consumption	CO_2 Production per Min in C c	O_2 Consumption per Min in C c	Respiratory Quotient	Calories per Sq M per Hr	Per Cent Below Average Basal Metabolism*	Minute Volume in Liters	Rate of Respiration per Min	Volume of Respiration per Min in C c	Pulse Rate per Min	Mg Non protein N per 100 C c Blood
3 48	162	190	0 85	33 8	—12	5 45	12 8	425	66	
3 61	157	192	0 82	33 9	—12	5 32	12 6	422	67	47 6
3 55	160	191	0 84	33 9	—12	5 39	12 7	424	67	
4 46	168	206	0 81	32 7	—16	4 62	13 1	351	69	
4 45	167	203	0 82	32 2	—16	4 55	13 1	346	68	45 5
4 46	168	205	0 82	32 5	—16	4 59	13 1	349	69	
4 31	180	235	0 76	33 9	—10	5 46	18 5	295	56	
4 33	182	234	0 79	33 9	— 9	5 43	18 9	289	56	33 0
4 31	180	235	0 76	33 9	—10	5 46	19 1	282	58	
4 32	181	235	0 77	33 9	—10	5 45	18 8	289	57	
4 07	176	229	0 77	33 3	—11	5 62	18 0	311	49	
4 21	171	227	0 75	32 9	—12	5 40	18 3	294	53	
4 14	174	228	0 76	33 1	—12	5 51	18 2	303	51	

—Patients Receiving a Nuclein Rich Diet

O_2 Consumption	CO_2 Production per Min in C c	O_2 Consumption per Min in C c	Respiratory Quotient	Calories per Sq M per Hr	Per Cent Below Average Basal Metabolism*	Minute Volume in Liters	Rate of Respiration per Min	Volume of Respiration per Min in C c	Pulse Rate per Min	Mg Non protein N per 100 C c Blood
3 63	160	183	0 87	32 9	—15	5 05	11 8	428	65	
3 69	161	187	0 87	33 7	—13	5 05	11 6	459	66	58 8
3 51	164	187	0 88	33 7	—13	5 33	11 5	439	66	
3 61	162	186	0 87	33 4	—14	5 14	11 6	442	66	
4 22	161	197	0 82	31 4	—18	4 67	12 8	363	68	
4 16	163	197	0 82	31 4	—18	4 74	12 8	377	69	46 7
4 19	162	197	0 82	31 4	—18	4 71	12 8	370	69	
4 11	168	214	0 78	31 1	—17	5 20	15 5	335	49	
4 31	176	223	0 79	32 5	—13	5 18	14 1	417	49	37 5
4 21	172	219	0 79	31 8	—15	5 19	15 5	376	49	
4 29	178	225	0 79	32 7	—13	5 25	17 9	292	49	
4 19	173	216	0 80	31 4	—16	5 14	17 2	296	49	
4 24	176	221	0 80	32 1	—15	5 20	17 6	294	49	

negative The blood pressure was 135 mm systolic and 95 mm diastolic The urine contained no casts, no blood, and no epithelium A scant trace of albumin was found once in the examination of several urine specimens Phenolsulphonephthalein excretion for two hours was 42 per cent Renal studies in this case have been reported by one of us[8]

The patient was placed on a purin-free diet May 17, 1917 He developed a mild gouty attack which affected the right hand, and, to a less degree, the right knee and elbow on May 19 and 20 On May 21 the attack had subsided

Case 3—J G Med No 6320 White, male, aged 58 Admitted to the Peter Bent Brigham Hospital March 23, 1917, and discharged April 11, 1917 Diagnosis Gout, arteriosclerosis, hypertension, chronic myocarditis, very questionable chronic nephritis

The patient used beer freely He had had about sixteen attacks of severe polyarthritis of gouty character during the previous twenty-six years Physical examination showed numerous tophi in the ears and fingers The joints showed the changes of a chronic arthritis The radial artery walls were sclerosed Blood pressure was 185 mm systolic and 117 mm diastolic Otherwise, physical examination was negative Urine examinations were negative Phenolsulphonephthalein excretion was 52 per cent in two hours Renal studies in this case have been reported by one of us[8]

Case 4—F J S Med No 6154 White, male, aged 43 Diagnosis Gout, obesity

The patient's habits were good During the previous ten years he had had numerous attacks of arthritis in one or several joints of the lower extremities Physical examination was essentially negative There were no signs of cardiovascular disease Blood pressure was 130 mm systolic and 90 mm diastolic A tophus was present in the right ear and from it sodium urate crystals were obtained The urine contained a scant trace of albumin, but no other pathologic elements were found Phenolsulphonephthalein excretion was 50 per cent in two hours Renal studies in this case have been reported by one of us[7]

EXPERIMENTAL FINDINGS

The results obtained in the study of the gaseous metabolism of the three gouty patients who received a purin-free diet are given in Table 1

A study of the table shows that the respiratory quotients are not abnormal The heat production and the percentage of the basal metabolism are lower in all cases than the average normal But they are not far enough removed from the normal to be significant of any disturbance in intermediary metabolism The blood shows a slight retention of nonprotein nitrogenous substances in Cases 1 and 2

In Cases 1, 2 and 3 the patients were fed 150 gm of sweetbreads daily for from two to five days A second experiment was run on Case 3 (Experiment 4, Table 2) in which the patient received anchovies, beef liver and beef kidneys over a period of three days instead of sweetbreads The effect of nuclein-rich diets on the gaseous exchange in the three gouty cases is given in Table 2

A study of Table 2 shows no abnormalities in the respiratory quotients The heat production and the percentages of the basal metabolism are lower than the average normal A comparison of Table 2

with Table 1 shows no changes of significance in the respiratory quotients in the three cases of gout. The percentages of basal metabolism are lower in all cases after the feeding of nuclein-rich materials, but the differences are not great enough to be indicative of any disturbance in intermediary metabolism. To rule out a possible effect on metabolism of the thyroid gland contained in sweetbreads, control experiments were made on Case 3. Instead of sweetbreads the patient was given, over a period of three days, 88 gm. of anchovies, 500 gm. of beef liver, and 400 gm. of beef kidneys. On this diet the basal metabolism of Case 3 was 3 per cent. lower (Experiment 4, Table 2) than when a purin-free diet was fed (Experiment 4, Table 1). From this result it is concluded that the thyroid gland fed in the other experiments (Experiments 1, 2 and 3 of Table 2) did not appreciably affect metabolism.

TABLE 3.—BASAL METABOLISM, MAY 20, 1917, OF CASE 2 DURING AN ACUTE ATTACK OF GOUT

Patient's height, 177.5 cm., weight 65.8 kg., surface area, 1.82 sq. m., Temp. (r) 99.8 F.

Period	CO_2 Production, per Cent	O_2 Consumption, per Cent	CO_2 Production per Min in C.c.	O_2 Consumption per Min in C.c.	Respiratory Quotient	Calories per Sq. M. per Hr.	Per Cent Below Average Basal Metabolism*	Minute Volume in Liters	Rate of Resp. per Min.	Volume of Resp. per Min.	Pulse Rate per Min.	Time of Experiment Period in Min.
I	3.41	4.33	191	242	0.79	38.3	—1	5.00	17.8	315	90	10.03
II	3.26	4.13	186	235	0.79	37.2	—3	5.70	16.8	339	92	9.98
Average	3.34	4.23	189	239	0.79	37.8	—2	5.65	17.3	327	91	

* Basal metabolism calculated according to the linear formula of DuBois.

A metabolism experiment was made during the time the patient, Case 2, was suffering with a mild attack of gout. The patient was receiving a purin-free diet. The findings are tabulated in Table 3.

The respiratory quotient, although slightly lower than in the other two experiments (Tables 1 and 2) on this patient, is not abnormal. The heat production and total metabolism percentages are just below the average normal figures for a man of 44. The heat production, however, is 6.2 calories more per hour and the total metabolism 15 per cent. higher than in the two previous experiments on this patient (Experiments 2 in Tables 1 and 2). The significance of this finding will be discussed later.

The gaseous metabolism of gouty Case 4 was studied. A synopsis of the report of this case has already been given. The patient was receiving a mixed diet. The findings are given in Table 4.

TABLE 4—Basal Metabolism, July 4, 1917, of Gouty Patient 4, After Receiving a Mixed Diet

Patient's height, 165 5 cm , weight 122 2 kg , surface area, 2 3 sq m , Temp (r) 98 6 F

Period	CO_2 Production, per Cent	O_2 Consumption, per Cent	CO_2 Production per Min in C c	O_2 Consumption per Min in C c	Respiratory Quotient	Calories per Sq M per Hr	Per Cent Below Average Basal Metabolism*	Minute Volume in Liters	Rate of Resp per Min	Volume of Resp per Min	Pulse Rate per Min	Time of Experiment Period in Min
I	3 05	3 85	203	256	0 79	32	—17	6 66	19 3	346	76	9 95
II	3 16	3 93	206	256	0 80	32	—17	6 51	12 2	529	69	10 1
Average	3 11	3 89	205	256	0 80	32	—17	6 59	15 8	438	73	

* Basal metabolism calculated according to the linear formula of DuBois

The respiratory quotient (Table 4) is not abnormal The heat production is low and the percentage of basal metabolism is 17 per cent below the normal average This, however, cannot be considered as abnormal

Throughout the stay of Patient 2 in the hospital the daily amount of uric acid excreted was determined This was done in order to be sure that a faulty uric acid elimination occurred after the feeding of sweetbreads The significance of the findings will be discussed later The results are given in Table 5

TABLE 5—Uric Acid Excretion After the Feeding of Sweetbreads in Gout Case 2

Date	Amount of Urine in C c	Gm of Uric Acid in Urine	Remarks
5/19/17	1,140	0 29	Acute gouty attack
5/20/17	1,015	0 28	Acute gouty attack
5/21/17	1,000	0 24	Attack subsided
5/22/17	900	0 20	
5/23/17	1,235	0 28	
5/24/17	1,110	0 21	
5/25/17	1,080	0 20	Fed 150 gm sweetbread
5/26/17	1,350	0 27	Fed 150 gm sweetbread
5/27/17	1,520	0 30	
5/28/17	1,300	0 45	

The feeding of sweetbreads produced a slight increase in the amount of uric acid excreted on the third day after the last feeding, as is shown by a study of Table 5

SUMMARY AND DISCUSSION

Normal respiratory quotients were obtained in the determination of the gaseous exchange in the lungs of our four gouty patients The variations in the basal metabolism from the average normal which were found in the experiments are not greater than have been reported for normal men,[4] although they were all at the lower limits of normal

The basal metabolism of different normal persons shows a variation of at least 20 per cent [4] For this reason minor departures in the basal metabolism of any one person from the average obtained by the study of a number of healthy people are not of any significance On the other hand, the basal metabolism of the same adult when performed on different dates shows a rather narrow range of variation provided the experimental conditions are the same For this reason minor changes in the basal metabolism of one person which result from differences in experimental conditions have considerable significance If nuclein-rich foods affected to any great extent the whole intermediary metabolism of gouty persons, the basal metabolism during periods of nuclein-rich diet would show differences as compared with the basal metabolism of the same individual on nuclein-poor diet In our three gouty persons, after adding nuclein-rich material to their diet, variations in the basal metabolism of 2 per cent (Cases 1 and 2) and of 3 per cent and 5 per cent (Case 3) occurred These differences, however, are very slight, and it cannot be held that these variations are great enough to signify an abnormality in the basal metabolism of these patients

Case 1 showed a definite increase in the nonprotein nitrogenous substances of the blood after the ingestion of sweetbreads The fact that but a very slight change occurred in the two basal metabolism experiments (Tables 1 and 2) on this patient indicates that the increase noted in the blood nonprotein nitrogenous substances was the result of retention by the kidneys and not of a derangement in metabolism

In Case 2 the daily output of uric acid in the urine was determined The ingestion of sweetbreads produced only a slight increase in the amount of uric acid excreted (Table 5) Such a faulty elimination of uric acid in gouty persons has been considered by most observers[2, 3] as evidence of a disturbance in the intermediary metabolism in gout Our studies on Case 2 (Tables 1 and 2), however, failed to detect any change attributable to a disturbance in metabolism Therefore, our results are evidence, although they do not completely exclude the possibility, that there is no derangement in the intermediary metabolism of the nucleins in gouty persons

Our results show that in chronic gout, in the absence of acute symptoms, and with patients on a purin-free or nuclein-rich diet, there is

no profound change in the intermediary metabolism as compared with that of a nongouty person Our negative findings do not exclude the possibility that in gout there is (1) a disturbance in the metabolism of the nucleins, (2) or a disturbance in some other phase of the intermediary metabolism, (3) or a disturbance in some minor phase of intermediary metabolism produced by nuclein-rich foods They only show that it is too slight, or of a nature not to produce any marked change in the basal metabolism

In Case 2 the basal metabolism was distinctly increased during the acute attack of gout (Table 3) At this time the rectal temperature was higher than when the other experiments (Tables 1 and 2) were made Therefore, this rise in the basal metabolism is not a specific effect of a gouty attack, but is comparable to any condition which increases metabolism to cause an increase in a patient's temperature

CONCLUSIONS

1 The basal metabolism of gouty persons falls within normal limits

2 The respiratory quotient of gouty persons falls within normal limits

3 Nuclein-rich foods produce no change in intermediary metabolism of gouty persons detectable by the method of indirect calorimetry

It is a pleasure to acknowledge the cooperation and help of Dr F W Peabody in this work, and we are indebted to Miss B I Barker for much assistance

THE EFFECT OF DIET ON BLOOD SUGAR IN DIABETES MELLITUS [*]

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This investigation was undertaken partly on account of its physiologic interest and partly in the hope that it might yield information which would enable the clinician to interpret blood sugar values taken at any time of the day The blood sugar was determined at hourly intervals in cases of diabetes mellitus These patients were ordered diets which were adjusted to the therapeutic needs of the individual. That is, the diets were either "carbohydrate-free," containing no starch except that found in green vegetables, or, save for a very few instances, limited in starch content, so that the glycosuria was held in abeyance or at a low level The results obtained under these circumstances, while they do not exhaust the subject from the physiologic or pathologic-physiologic point of view, are applicable to the practical interpretation of blood sugars in the treatment of diabetes mellitus The method of Lewis and Benedict[1] was employed to determine the blood sugar, Benedict's[2] modification of Fehling's solution was used in estimating the sugar in the urine

It is well known that the ingestion of glucose or a meal high in carbohydrate will increase the blood sugar in every human being, whether diabetic or not, however, normal individuals do not have a rise in their blood sugar after taking either protein or fat This fact has been determined by Jacobsen,[3] Strouse,[4] and Rolly and Oppermann,[5] and is substantiated in the present investigation There is no evidence in a normal person of a hyperglycemia when the blood sugar is taken at frequent intervals after a single large carbohydrate-free meal (Table 1), nor if determined in hourly specimens throughout the course of the day when three such meals are given (Tables 2 and 3) These experiments may be considered as controls for the observations made on the cases of diabetes mellitus

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* From the Medical Clinic of The Johns Hopkins Hospital

1 Lewis and Benedict Jour Biol Chem, 1915, **20,** 61

2 Benedict Jour Biol Chem, 1911, **9,** 57

3 Jacobsen, A Biochem Ztschr, 1913, **56,** 471

4 Strouse, S, Stein, I, and Wiseley, A Bull Johns Hopkins Hosp, 1915, **26,** 211

5 Rolly, F, and Oppermann Biochem Ztschr, 1913, **49,** 278

Time	Blood Sugar, per Cent	Diet			
		Protein	Fat	Carbohydrate	Total Calories
9 27 a m	0 10*				
10 00 to 10 °0		67	59	4	840
10 31	0 10				
10 51	0 10				
11 10	0 09				
11 36	0 10				
12 16 p m	0 10				
12 48	0 10				
1 57	0 10				
2 53	0 12				

Table 1—Blood sugar determinations at frequent intervals in a normal individual after a large carbohydrate-free meal There is no evidence of any increase in the glycemia

* Fasting

Time	Blood Sugar, per Cent	Diet			
		Protein	Fat	Carbohydrate	Total Calories
9 05 a m	0 12*				
9 35 to 9 50		30	42	3	526
10 33	0 12				
11 38	0 12				
12 20 to 12 35 p m		34	13	3	273
1 06	0 12				
2 09	0 12				
3 09	0 09				
4 10	0 12				
5 00 to 5 20		30	45	0	960
6 20	0 12				
8 30	0 12				

Table 2—Blood sugar determinations at hourly intervals in a normal individual on a carbohydrate-free diet There is no evidence of any change in the level of blood sugar throughout the day

* Fasting

Time	Blood Sugar, per Cent	Diet			
		Protein	Fat	Carbo hydrate	Total Calories
9 12 a m	0 12*				
9 30 to 9 45		30	42	3	526
10 37	0 12				
11 41	0 12				
12 20 to 12 35 p m		25	10	10	237
1 08	0 12				
2 10	0 12				
3 12	0 10				
4 13	0 12				
5 05 to 5 14		45	51	10	700
6 25	0 12				
8 30	0 12				

Table 3—Blood sugar determinations at hourly intervals in a normal individual on a carbohydrate-free diet There is no evidence of any change in the level of blood sugar throughout the day

* Fasting

Time	Blood Sugar, per Cent	Diet				Urine Glucose, Gm	
		Protein	Fat	Carbo hydrate	Total Calories	For Period	Per Hour
8 15 a m	0 16*						
9 25 to 9 34		19	34	45	579		
6 00 to 10 35						3 02	0 66
10 52	0 23						
11 50	0 23						
11 53 to 12 17 p m		60	26	116	963		
12 30						3 00	1 82
1 20	0 23						
2 23	0 26						
2 25						6 81	3 55
3 25	0 26						
3 27						6 71	6 48
4 42	0 26						
4 45						5 23	4 02
5 18 to 5 34		24	50	75	871		
6 30	0 26					5 78	3 31
7 50	0 32						
6 00 a m						40 32	3 51
9 00	0 21*						

Table 4—Blood sugar determinations at hourly intervals in a case of diabetes mellitus on a diet containing considerable starch The level of blood sugar rises successively after each meal There is a large quantity of sugar in the urine

* Fasting

Time	Blood Sugar, per Cent	Diet			
		Protein	Fat	Carbo hydrate	Total Calories
9 24 a m	0 15*				
9 50 to 10 20		77	79	14	1,108
10 28	0 15				
10 47	0 15				
11 08	0 18				
11 34	0 18				
12 13 p m	0 18				
12 47	0 15				
1 53	0 15				
2 51	0 15				
4 24	0 15				

Table 5—Blood sugar determinations at frequent intervals in a case of diabetes mellitus after a large carbohydrate-free meal There is a distinct rise of blood sugar forty-eight minutes after the meal is taken This hyperglycemia is maintained at least one hour and five minutes

* Fasting

Time	Blood Sugar, per Cent	Diet			
		Protein	Fat	Carbo hydrate	Total Calories
11 04 a m	0 18*				
11 35 a m to 12 05 p m		77	79	14	1,108
12 19	0 18				
12 51	0 23				
1 24	0 23				
2 38	0 19				
3 35	0 16				
4 46	0 18				

Table 6—Blood sugar determinations at frequent intervals in a case of diabetes mellitus after a large carbohydrate-free meal There is a distinct rise of blood sugar forty-six minutes after the meal is taken This hyperglycemia is maintained at least thirty-three minutes

* Fasting

In interpreting blood sugars obtained in diabetic individuals the clinician often takes for granted that every meal will result in an increase in the glycemia, so that the glucose in the blood will reach its maximum by steplike gradations in the evening This conclusion, thus far, rests on what seems to be obvious reasoning, but not on

Time	Blood Sugar, per Cent	Diet			
		Protein	Fat	Carbo hydrate	Total Calories
9 35 a m	0 07*				
9 55 to 10 20		77	79	14	1,108
10 35	0 07				
10 52	0 07				
11 10	0 09				
11 35	0 09				
12 22 p m	0 09				
1 25	0 11				
2 20	0 11				

Table 7—Blood sugar determinations at frequent intervals in a case of very mild diabetes mellitus after a large carbohydrate-free meal There is a slight rise of blood sugar at the end of fifty minutes This not only persists, but increases during the next three hours and ten minutes, when the observation is terminated

* Fasting

Time	Blood Sugar, per Cent	Diet			
		Protein	Fat	Carbo hydrate	Total Calories
9 15 a m	0 11*				
9 35 to 10 10		77	79	14	1,108
10 15	0 13				
10 36	0 10				
10 52	0 11				
11 13	0 10				
11 44	0 11				
12 22 p m	0 11				
1 25	0 11				
3 06	0 10				
4 10	0 10				

Table 8—Blood sugar determinations at frequent intervals in a case of diabetes mellitus after a large carbohydrate-free meal There is a slight, very transient, rise of blood sugar immediately following the intake of food Hourly determinations of blood sugar would have missed this glycemia

* Fasting

Time	Blood Sugar, per Cent	Diet				Urine
		Protein	Fat	Carbohydrate	Total Calories	
8 50 a m	0 18*					Contains no sugar on this day
9 00		20	32	0	380	
10 00	0 17					
11 00	0 18					
12 00 m	0 17					
12 10 p m		32	44	7	569	
1 00	0 17					
2 00	0 17					
3 00	0 17					
4 20	0 13					
5 00		24	24	6	346	
6 20	0 17					
8 40	0 11					
8 50 a m	0 17*					

Table 9—Hourly blood sugar determinations in a case of diabetes mellitus while on a carbohydrate-free diet There is no rise in the blood sugar above the fasting level There is a tendency toward a diminished blood sugar in the afternoon and evening

* Fasting

experimental evidence Under certain conditions it holds true Thus, in Table 4 it is seen that the blood sugar rises after each meal, being 0 16 per cent, while fasting, 0 23 per cent after breakfast, 0 26 per cent after dinner, and 0 32 per cent after supper The fasting blood sugar determination of the next morning rises to 0 21 per cent, as compared to 0 16 per cent of the previous day This increase in the fasting blood sugar, as well as the marked glycosuria, indicates that the diet in this case is one which is most unsuitable to the needs of the patient The blood sugar curve, with its steplike rise after each meal, obtained during the day, is one which may be considered typical of diabetes mellitus while the patient is receiving far more starchy food than is indicated These, however, are not the conditions which ordinarily present themselves to the clinician, and to make a correct interpretation of blood sugar determinations made at various times of the day it is necessary to examine the results obtained in patients who are receiving the usual form of dietetic treatment As is well known, the rise of blood sugar after the ingestion of glucose or starch is very much prolonged in the diabetic individual as compared to the normal

Time	Blood Sugar, per Cent	Diet				Urine
		Protein	Fat	Carbohydrate	Total Calories	
8 55 a m	0 45*					Contains 6·5 gm of glucose on this day
9 17 to 9 30		20	32	0	380	
10 34	0 45					
11 55	0 45					
12 20 to 12 35 p m		36	14	6	302	
1 50	0 45					
2 55	0 45					
4 00	0 45					
5 00	0 45					
5 10 to 5 15		10	6	0	97	
7 05	0 45					
11 35	0 45					
8 30 a m	0 45*					

Table 10—Hourly blood sugar determinations in a case of diabetes mellitus Case complicated by an infected gangrenous process of one foot and by myocardial insufficiency There is no change in the level of the blood sugar following the intake of a carbohydrate-free diet of rather low caloric value

* Fasting

Time	Blood Sugar, per Cent	Diet				Urine
		Protein	Fat	Carbohydrate	Total Calories	
8 30 a m	0 23*					Contains no sugar on this day
9 00 to 9 15		29	32	0	380	
10 00	0 23					
11 45	0 23					
12 45 p m	0 23					
2 00 to 2 20		46	56	10	750	
3 20	0 23					
6 00 to 6 25		33	37	9	516	
6 46	0 19					
7 20	0 23					
8 30	0 23					
9 50 a m	0 23*					

Table 11—Hourly blood sugar determinations in a case of diabetes mellitus while on a carbohydrate-free diet There is no rise in the blood sugar above the fasting level as the result of food ingestion

* Fasting

Time	Blood Sugar, per Cent	Diet				Urine
		Protein	Fat	Carbo hydrate	Total Calories	
8 50 a m	0 33*					Contains 50 gm of glucose on this day
9 40 to 9 50		20	32	0	380	
10 50	0 33					
11 50	0 33					
11 55 to 12 20 p m		23	65	7	728	
3 00	0 32					
4 05	0 33					
4 50 to 5 00		26	22	6	336	
6 35	0 28					

Table 12—Hourly determinations of blood sugar in a case of diabetes mellitus while on a carbohydrate-free diet The blood sugar throughout the day does not rise above the fasting level, although the initial blood sugar is high and there is a glycosuria

* Fasting

Time	Blood Sugar, per Cent	Diet				Urine
		Protein	Fat	Carbo hydrate	Total Calories	
8 11 a m	0 18*					Contains no sugar on this day
8 30 to 8 45		30	36	0	458	
9 45	0 18					
11 00	0 18					
11 50	0 18					
12 15 to 12 35 p m		47	54	19	77[illegible]	
1 20	0 18					
2 20	0 19					
3 25	0 18					
4 50 to 5 10		50	53	7	727	
6 40	0 18					
8 55	0 18					
8 00 a m	0 18*					

Table 13—Hourly determinations of blood sugar in a case of diabetes mellitus while on a carbohydrate-free diet The level of the blood sugar remains virtually constant throughout the day

* Fasting

Time	Blood Sugar, per Cent	Diet				Urine
		Protein	Fat	Carbohydrate	Total Calories	
8 16 a m	0 17*					Contains 30 6 gm of glucose on this day
9 25 to 9 37		30	42	3 0	526	
10 30	0 17					
11 45	0 17					
11 50 to 12 10 p m		53	59	10 0	807	
1 10	0 18					
2 25	0 18					
3 20	0 18					
4 20	0 18					
4 50 to 5 10		33	41	13 0	570	
6 35	0 18					
8 30	0 18					
7 55 a m	0 16*					

Table 14—Hourly blood sugar determinations in a case of diabetes mellitus while on a carbohydrate-free diet Although the diet slightly exceeds the patient's carbohydrate tolerance, as shown by the sugar in the urine, the blood sugar level is scarcely raised throughout the day

* Fasting

This fact has been fully established by the findings of many observers [6] Recognizing the fact that the glycemia may rise as the result of food intake, and subsequently fall, it becomes necessary to ascertain whether the hourly determinations of blood sugar, as used in the present observations, are sufficiently frequent to detect any changes that are likely to occur after starch-free food This question was determined by giving a diabetic individual a single large carbohydrate-free meal and estimating the blood sugar at frequent intervals It has already been shown that in a normal person no hyperglycemia is demonstrable under these conditions (Table 1) In the diabetic, however, there may be a distinct, though often slight, rise in the blood sugar (Tables 5 to 8) When the percentage of glucose does rise it seems to remain at its maximum for a considerable period (Tables 5, 6 and 7) It must be admitted that occasional slight transient rises of blood sugar occur after the taking of carbohydrate-free food, which would escape observation if the glycemia were determined at greater than fifteen-minute intervals (Table 8) Taking all the facts into consideration, however,

6 Tachau, H Deutsch Arch f klin Med, 1911, **104,** 437 Jacobsen, A Biochem Ztschr, 1913, **56,** 471 Hopkins, A H Am Jour Med Sc, 1915, **149,** 254 Hamman, L, and Hirschman, I To be published

it appears justifiable to conclude that blood sugar estimations made at approximately hourly intervals will reveal the more significant changes in the blood sugar level brought about by carbohydrate-free diets or meals low in starch, in cases of diabetes mellitus

The examination of the results in cases in which the blood sugar was determined at hourly intervals throughout the day reveals the fact

Time	Blood Sugar, per Cent	Diet				Urine Glucose, Gm per Hour
		Protein	Fat	Carbohydrate	Total Calories	
7 50 a m	0 12*					
8 00						+
8 18 to 8 22		16	27	16	382	
9 00						0 64
9 25	0 19					
10 00						1 10
10 30	0 18					
11 00						1 12
11 30	0 16					
11 55 a m to 12 10 p m		42	39	22	625	
12 00						1 31
1 00						1 89
1 10	0 19					
2 00						1 29
2 10	0 20					
3 00						1 71
3 10	0 18					
4 00						1 37
4 30	0 16					
5 00						1 10
5 08 to 5 15		39	26	22	492	
6 00						0 50
6 30	0 14					
7 00						0 56
8 00						1 08
8 30	0 16					
8 00 p m to 6 00 a m						Trace
7 40 a m	0 14*					

Table 15—Hourly determinations of blood sugar in a case of exophthalmic goiter and diabetes mellitus while on a diet containing a small amount of starch There is a distinct rise of blood sugar after breakfast, which is slightly exceeded after the midday meal and diminishes after supper

* Fasting

Time	Blood Sugar, per Cent	Diet				Urine
		Protein	Fat	Carbo hydrate	Total Calories	
8 30 a m	0 15*					Contains no sugar except for a trace of glucose in the specimen voided from 6 45 to 8 13 p m
8 58		23	33	16	467	
10 15	0 19					
11 20	0 19					
12 15 p m	0 15					
12 20		50	42	22	686	
2 00	0 19					
3 00	0 18					
4 05	0 13					
5 15	0 11					
5 45		36	29	6	442	
6 45	0 15					
8 30	0 17					

Table 16—Hourly determinations of blood sugar in a case of exophthalmic goiter and diabetes mellitus This observation was made after partial thyroidectomy, that of Table 15 before the operation There is a distinct rise of blood sugar after breakfast, which is the maximum attained in the course of the day

* Fasting

that many of these exhibit no rise above the fasting level (Tables 9, 10, 11 and 12), or only a very slight increase of 0 01 per cent (Tables 13 and 14), while others (Tables 15 to 20, inclusive) give evidence of a considerable elevation in the blood sugar as the result of the intake of food

It is readily seen that if the blood sugar rises at all, the most notable increase occurs within an hour or two after breakfast There may in some instances be a further rise in the course of the day, but this is of comparatively small moment, since the initial increment after breakfast varies from 0 02 to 0 09 per cent, while the highest subsequent increase surpasses these by only 0 02 per cent (Tables 15 to 20, inclusive, also Table 21) Furthermore, it may be noted that, especially in the afternoon or evening hours, the blood sugar shows a tendency to diminish This is true when there is an increase after breakfast (Tables 15, 16, 18, 19 and 20), and also when this does not occur (Tables 9, 11 and 12) It may, therefore, be concluded that the maximal rise (or a rise approaching the maximal) of blood sugar occurs in diabetic patients on a carbohydrate-free diet, or one containing a moderate amount of starch, about one hour after breakfast If it is the aim of the clinician to determine the maximal blood sugar per-

Time	Blood Sugar, per Cent	Diet				Urine
		Protein	Fat	Carbo hydrate	Total Calories	
8 40 a m	0 14*					Contains no sugar on this day
8 45		27	32	0	408	
10 00	0 16					
11 00	0 16					
11 50		60	41	10	668	
12 00 m	0 16					
1 15 p m	0 16					
2 15	0 18					
3 27	0 16					
4 30	0 16					
4 45		49	24	12	473	
5 55	0 16					
8 00	0 16					
8 55 a m	0 18*					

Table 17—Hourly blood sugar determinations in a case of diabetes mellitus while on a carbohydrate-free diet The blood sugar rises after breakfast This rise is exceeded only once during the day, after the noon meal

* Fasting

Time	Blood Sugar, per Cent	Diet				Urine
		Protein	Fat	Carbo hydrate	Total Calories	
8 20 a m	0 13*					Contains 12 gm of glucose on this day
9 00 to 9 15		29	42	0	510	
10 10	0 16					
11 30	0 14					
12 30 p m	0 13					
12 30 to 12 45		44	71	7	869	
1 55	0 14					
3 00	0 12					
4 00	0 08					
5 15 to 5 30		25	27	5	374	
6 45	0 15					
8 45	0 18					
8 35 a m	0 15*					

Table 18—Hourly blood sugar determinations in a case of diabetes mellitus while on a carbohydrate-free diet The blood sugar in this patient rises slightly higher after the last meal of the day than after breakfast

* Fasting

centage occurring in any individual, this is probably the most favorable time to obtain it, since in the afternoon and evening hours the blood sugar percentage has a distinct tendency to diminish, and thus may lead to an erroneous interpretation

From the point of view of pathologic physiology, some interesting conclusions may be drawn from these observations It is perfectly clear that in these cases which are being treated by a diet restricted in carbohydrates, each successive meal does not produce an increment of

Time	Blood Sugar, per Cent	Diet				Urine
		Protein	Fat	Carbo hydrate	Total Calories	
9 15 a m	0 16*					Contains 4 gm of glucose in the corresponding 24 hour specimen
9 20		21	13	58	445	
10 25	0 25					
11 20	0 23	20	20	72	567	
12 15 p m	0 23					
1 55	0 23					
3 05	0 22					
4 00		7	8	17	173	
4 20	0 22					
5 00		19	17	40	400	
5 40	0 22					
6 50	0 26					
8 10	0 23					
9 05 a m	0 15*					

Table 19—Hourly blood sugar determinations in a case of diabetes mellitus Patient on a diet containing a moderate amount of starch, a little above the patient's carbohydrate tolerance There is a marked rise of blood sugar after breakfast, which is surpassed by only a very slight margin at 6 50 p m

* Fasting

blood sugar This is contrary to the usual conception of the course of events, and the picture presented is quite different from that found in patients indulging in a high carbohydrate diet (Table 4) Hamman and Hirschman[7] have demonstrated that superimposed doses of glucose are not necessarily followed by a steplike rise in the blood sugar It is only the first dose that causes the blood sugar percentage to rise, the subsequent ones apparently have no effect This substantiates the present findings

7 Hamman, L, and Hirschman, I I · Studies on Blood Sugar, The Archives Int Med, 20, 761

A hypothesis suggests itself which may explain these phenomena In Table 21, which summarizes the cases studied, it may be noted that the blood sugar values remain at the fasting level or below it throughout the day in those cases in which the initial hyperglycemia is marked (0 17 to 0 45 per cent, Tables 9 to 14), whereas, it rises in those in which it is low (0 12 to 0 16 per cent, Tables 15 to 20) It seems that each diabetic has a blood sugar level at which his carbohydrate metabolism proceeds in a fairly normal manner, with no rise in the blood sugar after meals of a moderate starch content In very mild cases this acquired blood sugar level may be very low and no increase result after eating a starch-free meal, whereas, in individuals with a very marked derangement in their carbohydrate metabolism, such a favorable blood sugar level will be proportionately increased When this optimum glucose percentage in the blood is reduced by dietary restrictions, the organism tends to respond by a hyperglycemia on the least provocation It is under such circumstances that there occurs an increase in the glucose of the blood after the ingestion of protein and fat Such reactions may go very far to explain the very wide variations in blood sugar often found in cases of diabetes [8]

Time	Blood Sugar, per Cent	Diet				Urine
		Protein	Fat	Carbohydrate	Total Calories	
8 00 a m	0 14*					Contains no sugar on this day
8 20 to 8 35		35	38	25	640	
9 36	0 16					
10 32	0 17					
11 32	0 14					
12 m to 12 30 p m		58	60	42	968	
1 30	0 17					
2 30	0 17					
3 33	0 17					
4 30	0 17					
5 15 to 5 35		41	50	41	801	
6 55	0 17					
8 30	0 15					

Table 20—Hourly determinations of blood sugar in a case of diabetes mellitus Patient on a diet containing a moderate amount of starch There is a rise of the percentage of blood sugar after breakfast which is not exceeded throughout the day

* Fasting

8 Mosenthal, H O, and Lewis, D S Bull Johns Hopkins Hosp, 1917, 28, 187

It has been shown previously by von Moraczewski[9] that the blood sugar rises after exercise, and that, in spite of this hyperglycemia, the tolerance for sugar is greater after muscular effort than during rest, when the blood sugar is lower This holds true, apparently, for the diabetic as well as for the normal individual Tests of the concentration of the blood in these experiments showed that there was no diminution in the hydremia through sweating, which might have been responsible for an apparent increase in the percentage value of the blood sugar Thus, it seems that the human organism is able to utilize glucose more effectively when the blood sugar is at a high level than at a low one This is frequently observed clinically and brings up the much debated question whether it is wise to attempt to reduce the blood sugar in every case of diabetes mellitus to a normal level From the facts given here it would appear that there are some arguments in favor of not carrying such an endeavor too far

Summary of Table	Blood Sugar per Cent						
	Fasting	After Breakfast		After Lunch		After Supper	
		Maximal	Minimal	Maximal	Minimal	Maximal	Minimal
9	0 18	0 18	0 17	0 17	0 13	0 17	0 11
10	0 45	0 45	0 45	0 45	0 45	0 45	0 45
11	0 23	0 23	0 23	0 23	0 23	0 23	0 19
12	0 35	0 33	0 33	0 33	0 32		0 28
13	0 18	0 18	0 18	0 19	0 18	0 18	0 18
14	0 17	0 17	0 17	0 16	0 18	0 18	0 18
15	0 12	0 19	0 16	0 20	0 16	0 16	0 14
16	0 15	0 19	0 15	0 19	0 11	0 17	0 15
17	0 14	0 16	0 16	0 18	0 16	0 16	0 16
18	0 13	0 16	0 13	0 14	0 08	0 18	0 15
19	0 16	0 25	0 23	0 23	0 22	0 26	0 22
20	0 14	0 17	0 14	0 17	0 17	0 17	0 15

Table 21—Summary from preceding tables Summary of the hourly determinations of blood sugar in cases of diabetes mellitus on a carbohydrate-free diet, or one containing a moderate amount of starch If there is a rise of blood sugar in the course of the day, the maximal value reached one or two hours after breakfast is usually not exceeded to any marked degree after lunch or supper There frequently is a diminution in the glycemia in the afternoon and evening

9 Von Moraczewski, W Berl klin Wchnschr, 1915, **52,** 1038, ibid, Ztschr f biol Chem, 1915, **71,** 268

SUMMARY

The maximal percentage of blood sugar occurring in diabetic individuals on a carbohydrate-free diet, or one containing a moderate amount of starch, can be obtained by making the determinations one to two hours after breakfast The glycemia may rise somewhat higher after lunch or supper, but never to any marked degree On the other hand, the blood sugar may fall considerably in the afternoon and evening hours, leading to erroneous interpretations if taken at this time of day (Table 21)

In diabetic cases there is a tendency for the blood sugar to remain constant throughout the day while on a protein-fat diet, if the fasting blood sugar is high, on the other hand, if the fasting blood sugar is low, that is, if it has been reduced by previous dietetic treatment, there is an increase which may become very marked in the glycemia after carbohydrate-free food (Table 21) This leads to the conclusion that cases of diabetes mellitus, in raising their fasting or basal blood sugar percentage, are trying to adjust their carbohydrate metabolism for the more advantageous utilization of glucose It may be desirable, therefore, not to attempt to reduce the blood sugar to a normal value in cases of diabetes mellitus

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STIMULATION OF THE RESPIRATION BY SODIUM CYANID AND ITS CLINICAL APPLICATION *

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The stimulation of the respiration by hydrocyanic acid has been known ever since its physiologic action was first investigated It was sought to utilize this extremely obvious stimulation of the respiration therapeutically, and we find articles published in the first half of the last century lauding its use as a respiratory stimulant [1] The depressing action of hydrocyanic acid was also noted [2] The only remnant of this once prominent remedy left in modern therapeutics is the use of hydrocyanic acid in certain cough mixtures

Geppert[3] established that the action of hydrocyanic acid is essentially asphyxiation, since it acts by decreasing the oxygen absorbed by the tissues and also the carbon dioxid produced by them

The attitude of modern pharmacologists on the therapeutic use of hydrocyanic acid may be gathered from the following

Heinz[4] says that hydrocyanic acid is one of the strongest stimulants for the respiration known, but that its stimulating action cannot be used in practice because it is too poisonous

Cushny[5] declares "Prussic acid might be eliminated from therapeutics without loss"

Sollmann[6] says "There seems to be no rational basis for the therapeutic use of cyanids"

Bastedo[7] makes virtually the same statement

It is our opinion that the disrepute into which hydrocyanic acid has fallen is due to the following (1) the fact that its action is fleeting, since it is apparently rapidly transformed into the nontoxic sulpho-

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* Submitted for publication Aug 21, 1917

1 Ryan Tr Coll Phys, 1828, **5**, 479

2 Magendie, F Physiological and Chemical Researches on the Use of Prussic Acid, etc, 1820, New Haven, Granville, A B Further Observations on the Internal Use of Hydrocyanic Acid (Prussic Acid), 1819, London, Coullon, J J A Considerations medicales sur l'acide prussique, 1808, Thesis Medicine, Paris

3 Geppert, J Ztschr f klin Med, 1889, **15**, 208, 307

4 Heinz Handbuch der Experimentellen Pathologie und Pharmakologie, Jena, 1906, 2, **1**, 588

5 Cushny, A R A Textbook of Pharmacology and Therapeutics Philadelphia, Lea & Febiger, 1915, p 453

6 Sollmann, T A Manual of Pharmacology Philadelphia, W B Saunders Company, 1917, p 617

7 Bastedo Materia Medica, Pharmacology Philadelphia, W B Saunders Company, 1913, p 403

cyanate, (2) the rate of absorption from the stomach is sufficiently uncertain so that either no effect follows its administration or too intense an effect is noted, (3) instability of all preparations of hydrocyanic acid, (4) the popular idea that the cyanids are so very poisonous [8]

We determined to investigate the subject from the standpoint of modern intravenous therapeutics, substituting sodium cyanid for hydrocyanic acid Sodium cyanid of fair purity is now on the market [9] This substance is perfectly stable in the solid state if kept in tightly stoppered, well filled bottles It is very soluble in water Our solutions were always freshly prepared, the oldest used by us having been prepared forty-eight hours before administration The sodium cyanid was dissolved in sterile physiologic salt solution

We prefer sodium cyanid to potassium cyanid because of the depressing effect of potassium salts on the heart The effect of the soluble cyanid is essentially the same as that of hydrocyanic acid

We have studied the stimulating action of sodium cyanid on the respiration in animals and in man A detailed statement of the work on animals will soon be published in the *Journal of Pharmacology and Experimental Therapeutics* However, a brief statement of the experimental work which preceded the clinical application of the method is essential The experiments were nearly all performed on dogs, only a few rabbits were used in the early part of the work The effect of sodium cyanid on the depressed respiration was determined under the following conditions [10] morphin poisoning, stoppage of respiration from

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8 The popular view that the cyanids are among the most poisonous substances known seems to be due to the statement by Magendie that animals, if given hydrocyanic acid, die as quickly as though they had been hit by a cannon ball While all will admit that fatal doses of hydrocyanic acid kill with great rapidity, the dose of the cyanids required to kill is far above that of many other substances The fatal dose of hydrocyanic acid is usually placed at from 30 to 100 mg, and the fatal doses of sodium cyanid and potassium cyanid on an equimolecular basis are, respectively, from 50 to 167, and from 72 to 240 mg Much greater quantities than this can be given in small divided doses over a longer period of time without deleterious effects, due to the rapid detoxification in the body

9 The sodium cyanid which we used was manufactured by Kahlbaum and contained from 92 to 95 per cent of sodium cyanid

10 A drug may be clearly indicated to modify abnormal functioning due to one cause and may be entirely worthless in the same form of abnormal function due to another cause For instance, in bradycardia due to excessive vagal tone, atropin is the only drug to be used to increase the pulse rate However, if the bradycardia is due to heart block atropin will be of no avail Again, digitalis is perhaps the first drug one would consider to reduce a rapid pulse rate It is the drug of choice if the rapid pulse is due to decreased vagal tone, low blood pressure and cardiac dilatation, but it is worse than useless in simple febrile tachycardia Any number of similar examples might be given, all of which indicate that in order to treat rationally a given abnormality of function we must know the cause of the abnormal function so far as we can analyze the condition

deep chloroform and ether anesthesia, hemorrhage, and increased intracranial pressure By far the greater part of the work was done on animals under increased intracranial pressure Such a condition is met with clinically as a result of basilar fracture, intracranial hemorrhage, brain tumors, etc In addition to determining the effect of sodium cyanid on the respiration under increased intracranial pressure, we studied the effect of the following drugs on the respiration under this condition for comparison with the cyanid, namely, caffein citrate, strychnin sulphate, atropin sulphate and lactic acid

In the experiments on increased intracranial pressure, a cranial cannula was put in place and the pressure transmitted by Ringer's solution Sixty-two experiments were performed under increased pressure Our method of experimentation in the main was as follows

The intracranial pressure was gradually increased to the point at which the respiration ceased The degree of anemia of the respiratory center at which all activity ceases varies in different animals and must be determined in each experiment Now, with this degree of anemia maintained, the drug whose effect on the respiration it was desired to study was injected intravenously, the dosage varying throughout the range of the probably useful amounts The results of the experimental work may be summarized as follows

1 Caffein citrate and atropin sulphate are useless in the treatment of respiratory depression due to increased intracranial pressure It seemed that the death of the animal was hastened by the administration of either of these drugs in sufficient quantities to have any observable effect

2 The action of lactic acid when administered under the conditions stated varies remarkably in different animals In some dogs no effect whatever was noted, while in others it proved to be quite an efficient stimulus to the respiration The stimulation lasted for quite a period of time, but in all cases the animal died from respiratory failure, and we do not consider lactic acid as a useful stimulant to the respiration under these conditions

3 Strychnin sulphate administered to dogs with the respiration depressed by increased intracranial pressure caused a distinct stimulation of the respiration The latent period of the stimulating action of strychnin averages twenty-seven seconds The stimulation lasted over a considerable period of time, the longest period of stimulation being twenty-eight minutes, after a single dose In many cases a peculiar type of group respirations was noted under strychnin

4 The result of intravenous administration of sodium cyanid to dogs under increased intracranial pressure may be briefly indicated as follows

(*a*) It causes stimulation of the respiration, when properly used, practically up to the time of the death, and is undoubtedly the strongest known stimulant to the respiration in this condition

(*b*) The average latent period of its action is from six to nine seconds

(*c*) The intensity and duration of the stimulation depends on the dose and rate of administration As a result of a single injection within a few seconds, the average duration of stimulation is from ten to fifteen seconds The longest period of stimulation following a single injection was one hour If too much sodium cyanid is given within a given period of time, a brief period of stimulation followed by depression will be noted

(*d*) By means of a slow continuous intravenous injection of sodium cyanid, a continuous stimulation of the respiration of almost any desired intensity may be obtained [11] A constant stimulation of the respiration was maintained for a period of two hours by a continuous slow intravenous injection of hundredth-normal sodium cyanid, with the intracranial pressure maintained at a level which had previously repeatedly been demonstrated to paralyze the respiration in the same animal In these slow continuous injections, every slight change in the rate of injection causes its corresponding change in the respiratory movements

(*e*) The margin of safety in the intravenous administration of sodium cyanid in dogs may be gathered from the following data

(1) The amount of sodium cyanid required to give a decided stimulation in a single rapid injection is approximately 0 1 c c per kilogram

(2) The amount of sodium cyanid required in a continuous slow injection to maintain a satisfactory stimulation under increased intracranial pressure, is 1 c c of a hundredth-normal solution in one and a half to three and a half minutes for a dog of about 10 kg

(3) It is well known that sodium cyanid is quickly transformed in the body to a nontoxic substance, supposedly the sulphocyanate We have endeavored to determine the rate at which it is detoxified in the organism by determining the maximum rate at which it can be injected intravenously without producing any symptoms whatever These observations were made on dogs which were not subjected to increased intracranial pressure, and the maximum rate at which a hundredth-normal solution of sodium cyanid may be injected without producing any symptoms whatever was found to be 1 c c per one and one-half minutes It would seem, therefore, that the animal under

11 The action of the cyanid in these experiments reminds one of the stimulation of the respiration by carbon dioxid

increased intracranial pressure is somewhat more sensitive to sodium cyanid than the normal anesthetized animal

(4) The fatal dose of hundredth-normal sodium cyanid rapidly injected from thirteen to twenty-five seconds intravenously is from 2.63 to 3.3 c.c. per kilogram of body weight. The smaller dose killed a dog in sixty-three minutes while the larger dose killed in twelve minutes.

Since 2 c.c. hundredth-normal sodium cyanid injected within three seconds caused stimulation even in our largest dogs, the therapeutic dose per kilogram may be placed at 0.1 c.c. per kilogram. Hence, twenty times the therapeutic dose when administered rapidly kills in about one hour.[12]

(*f*) As a result of our early experiences with sodium cyanid, showing how ephemeral is the stimulating effect of a single dose, we sought by means of administering sodium cyanid and strychnin sulphate in sequence to obtain a greater and more lasting stimulation of the respiration than could be obtained with either drug alone. Our work indicates, in the dog at least, under conditions of increased intracranial pressure that this is true. The later work on the slow continuous injections of sodium cyanid, however, causes us to attach somewhat less importance to the sodium cyanid-strychnin sequence. It may, however, prove to be a very useful method clinically.

(*g*) Under the condition of this work and the dosage here used we have found that sodium cyanid has remarkably little effect on the circulation. Thus the pulse rate is, in general, but slightly decreased, and the blood pressure but little altered.

CLINICAL WORK

Having convinced ourselves through our mammalian work that the margin of safety in the intravenous administration of sodium cyanid is ample for human therapy, it was determined, as opportunity presented itself, to study the therapeutic effect of sodium cyanid in suitable human cases such as the following: (1) cases of increased intracranial pressure from any cause which show depression of the respiration. It should be stated that we did not propose to use sodium cyanid when an operation for decompression was indicated, but simply to stimulate the respiration by sodium cyanid in the interim between the failure of respiration and the time when operative measures could be instituted; (2) failure of the respiration under chloroform and ether anesthesia; (3) in bedridden cases in advanced paresis when

12. Since the fatal injections were given over a longer period of time it may be that the exact margin of safety may be less. Further work must determine this.

a hypostatic pneumonia was in the process of developing In this instance it was hoped that the respiratory exercise induced by the sodium cyanid would improve the pulmonary condition and at least delay the fatal outcome

Accordingly, we made fifteen intravenous injections in ten cases

METHODS

Our first work indicated clearly that a fiftieth-normal solution of sodium cyanid is preferable to the hundredth-normal solution in human therapy A fiftieth-normal solution of sodium cyanid should contain 0 98 mg per cubic centimeter In our work, however, what we have called a fiftieth-normal solution was actually made up by dissolving 1 mg per cubic centimeter in physiologic salt solution The sodium cyanid was dissolved in sterile 0 9 per cent salt solution and was handled aseptically Since solid sodium cyanid is free from bacteria, it is unnecessary to sterilize after dissolving the sodium cyanid In fact, such a sterilization would change the concentration of the solution to such an extent that an analysis would have to be made to determine its strength It is, therefore, not permissible to sterilize the solution after dissolving the cyanid

TECHNIC

The injections were made with 20 c c record syringes, or from 50 c c burets The injections were all made in the median basilic vein In addition to the intravenous injections, several intramuscular injections were made, and in one case, through faulty technic, quite an amount of the fiftieth-normal sodium cyanid was injected into the perivascular tissue In no case was there any sign of inflammation or local irritation

The rate of administration is all important, and it is necessary to time the injection exactly This point will be brought out later

The respiration was recorded by means of a tambour One or two large, thin-walled volley-ball bladders were placed over the chest and abdomen and a canvas bandage fixed about the patient and the bladders The bladders were connected by a Y tube and then with the tambour by means of a rubber tube In the tables which follow we have recorded the respiratory rate before and after the administration of the drug, and also the total linear excursion of the lever of the tambour in centimeters in twenty seconds This latter figure would be an exact measure of the lung ventilation were our method of recording the respiration perfect This is not the case, however, but we regard the figure obtained as probably roughly proportional to the lung ventilation, or at least as near an approximation to it as we were able to obtain

A Jaquet time-marker recorded the time in seconds, and a marking pen was used to indicate any procedure The pulse was taken at the wrist throughout at intervals Systolic and diastolic blood pressure determinations were made in one case, but no change in the blood pressure was noted

CASES IN WHICH TREATMENT WAS ADMINISTERED

CASE 1—H H, man, aged 39, weight 160 pounds General state of nutrition good Heart enlarged, apex beat in sixth interspace beyond nipple line Loud blowing, systolic murmur, with maximum intensity at second interspace on right side and transmitted into vessels of the neck and the left axillary

space Murmur also heard at the apex Thickening of radial, brachial and temporal arteries

Diagnosis—Dementia paralytica

This patient received a total of 26 c c of fiftieth-normal sodium cyanid or 26 mg of sodium cyanid within a period of sixteen minutes The administration of 1 c c in thirty seconds was the slowest rate of injection that caused a stimulation of the respiration Injection of 1 c c per thirty, twenty, fifteen, twelve, and ten seconds caused increasing responses During the period in which he received 1 c c in fifteen seconds the rate remained unchanged, but the amplitude of the respiration doubled A series of injections of 1 c c at intervals of one-half minute each called forth a beautiful response, the amplitude again being increased without any change in the rate The duration of the stimulation following a single injection was approximately twenty seconds It was observable in this case that during marked stimulation the accessory respiratory muscles of the neck were used At the end of the injection some flushing of the face was noted

Case 2—E L E, man, aged 48, weight 90 pounds

Diagnosis—Dementia paralytica

The patient was bed ridden, semicomatose, and becoming progressively weaker It was impossible to arouse him, the eyes were constantly closed The patient was much emaciated

TABLE 1—Case 2, Treatment 1

May 18, 1917

No	Procedure N/50 NaCN, C c	Time	Respiration per 20 Seconds				Remarks
			Before		After		
			Rate	Vent	Rate	Vent	
1	2	2 09	6 0	6 0	6 0	8 9	Pulse 80 per min , 2 c c administered in 3 sec
2	3	2 10	6 0	5 5	6 5	13 5	Pulse 80 90 80 3 c c administered in 6 sec
3	3	2 13	6 5	5 3	7 5	16 0	Apnea of 15 sec followed stimulation, Figure 1, A 3 c c administered in 10 sec , pulse 84
4	5	2 16	6 0	5 3	8 0	21 9	5 c c administered in 7 sec , apnea of 32 sec followed stimulation, pulse during apnea 86, pulse when respiration was resumed 78, Figure 1, b
5	7	2 20	6 0	5 8	10 0	26 4	Pulse 88, apnea of 40 sec followed stimulation, during which pulse was 104, 7 c c were injected in 11 sec , after stimulation passed, respiratory rate was 5 in 20 sec , linear measure 4 8 cm , Figure 1, C
6	0 5 mg	2 27	6 0	6 1	5 0	5 0	Pulse 72
	strychnin sulphate	2 28			5 5	6 7	Pulse 66
		2 33			6 5	6 0	Pulse 70

Patient 2 received 20 c c fiftieth-normal sodium cyanid or 20 mg of sodium cyanid in a period of thirty-four minutes The apnea following each rapid injection of sodium cyanid is roughly proportional to the intensity of the stimulation of the respiration and this again is almost proportional to the dose of sodium cyanid and the rate of injection We therefore regard the respiratory pause following the stimulation as a true apnea This patient also received 0 5 mg of strychnin sulphate intravenously in a period of thirty-four minutes The strychnin did not stimulate the respiration There was a latent period of reaction to sodium cyanid of twenty-one seconds Increase in pulse rate 30 per cent

Case 2—*Treatment 2*—June 11, 1917 As the results of this treatment were similar to those in the first they are not tabulated The patient received 82 c c fiftieth-normal sodium cyanid or 82 mg of sodium cyanid in a period of forty-five minutes injected slowly The increase in the pulse rate was 23 per cent, and the latent period of reaction to the sodium cyanid thirteen seconds

TABLE 2—Case 2, Treatment 3

June 12, 1917 (Buret injection)

No	Procedure N/50 NaCN, C c	Time	Respiration				Remarks
			Before		After		
			Rate	Vent	Rate	Vent	
1	19 slowly	8 12	5	5 9	5	7 4	1 c c in 15 sec
					7	13 4	1 c c in 10 sec
					6	7 5	1 c c in 40 sec
					9	24 7	1 c c in 10 20 sec, total 19 c c in 6 min
					6	5 0	After cessation of injection
3	15 slowly	8 22½	5	4 0	6	11 5	2 c c in 20 sec
					7	11 7	1 c c in 15 to 20 sec
					7	6 8	1 c c in 25 sec
					9	22 2	1 c c in 20 sec Total 15 c c in 5 min 2 c c NaCN first injected to remove blood in needle Patient received 34 mg NaCN or 34 c c N/50 NaCN in 20 min (Demonstrated before the Dane County, Wis, Medical Society)

Case 2—*Treatment 4*—June 15, 1917 Two c c of fiftieth-normal sodium cyanid intravenously produced the same stimulating effect as in the first treatment, while 10 c c intramuscularly showed only a slight stimulating effect The patient received 40 c c fiftieth-normal sodium cyanid or 40 mg sodium cyanid in a period of forty minutes The latent period of reaction to the sodium cyanid was eighteen seconds

Case 3—C L E, man, aged 36, weight 135 pounds

Diagnosis—Dementia paralytica

The patient was bed ridden, unable to speak, and has convulsions, with brief intervals of relaxation between seizures

TABLE 3—Case 3

June 15, 1917

No	Procedure N/50 NaCN C c	Time	Respiration Before Rate	Before Vent	After Rate	After Vent	Remarks
3	2	2 18	7	4 9	8 0	6 4	1 c c in 10 sec
5	10 slowly	2 20¼	–	5 8	8 0	7 9	
6	5	2 25	7	6 8	8 0	10 4	Pulse 96
9	2	2 40	7	5 8	7 5	5 9	
10	9 slowly	2 41	8	6 0	9 0	9 0	1 c c in 14 sec
					12 0	12 4	Pulse 96 Total, 9 c c in 2 min
14	18	2 56	8	5 9	8 0	11 4	The 18 c c were given 1 c c at a time For effects note Figure 2
					8 0	7 8	
					10 0	9 1	
					11 0	9 6	Cough
					9 0	10 4	
26		3 06			10 0	10 2	Face flushed, total 18 c c in 10½ min
29	1	3 09¼	9	6 2	10 0	9 9	
30	1	3 11	8	5 2	10 0	10 8	
31	5 slowly	3 13	8	5 7	9 0	9 0	1 c c in 19 sec, total 5 c c in 1½ min pulse strong, 112
					10 0	10 5	
42	4 5 in muscle	3 46	7	6 9	7 0	7 9	
43	5 in muscle	3 48	8	6 7	8 0	8 2	Injection lasted ¼ min massaged point of injection
45	10 in muscle	3 55	8	6 0	4 0	8 4	
					10 0	9 85	Pulse 104, at 4 14 pulse was 96

Less muscle twitching when drug is being given Responds to call of name No convulsions precipitated by administration of drug Had many convulsive attacks in the previous few days Increase in pulse rate 16 per cent This patient received 72 5 c c fiftieth-normal sodium cyanid or 72 5 mg sodium cyanid in one hour and forty minutes Latent period of respiratory stimulation 11 seconds

CASE 4—G E F, man, aged 26, weight 140 pounds Heart normal in size Loud systolic murmur at apex transmitted to the left, audible along sternum and at base Blood pressure systolic 90, diastolic 50

Diagnosis—Dementia praecox, catatonic form

The patient was always very quiet, sat by himself, made no effort to speak to any one and could not be induced to answer questions Had become emaciated

TABLE 4—CASE 4

June 15, 1917

No	Procedure N/50 NaCN, C c	Time	Respiration Before Rate	Respiration Before Vent	Respiration After Rate	Respiration After Vent	Remarks
3	2	4 32¾	4 0	3 8	5 0	5 7	
4-7	8	4 33¼			4 0	4 9	Total 8 c c in 2¾ min (2 c c at a time), pulse 52
8	2	4 37	4 0	4 9	5 0	6 4	
9	8	4 38¼	3 5	4 0	4 5	7 8	Total 8 c c in 3½ min (5 c c, 1 c c, and 2 c c)
14	5	4 46¾	3 5	4 2	4 0	8 1	
15	2	4 49¼					
16	2	4 51¼	4 0	3 8	4 0	5 45	
17	12 slowly	4 52½	4 0	3 65	4 0	10 7	1 c c in 9 sec
					6 0	8 85	1 c c in 15 to 20 sec, respirations very regular, pulse 128
19		4 58½					Pulse 100 at 4 58½, 88 at 5 00¾, and 86 at 5 02
22	2	5 10	4 0	4 15	4 0	6 1	Pulse, 72 before injection, 84 after injection
23	2	5 12	4 0	4 9	4 0	6 5	
24	2	5 13¾	4 0	3 8	4 0	7 0	
25	6 slowly	5 15¼	4 0	4 15	4 0	8 4	1 c c in 16 sec, respiration very regular, pulse 100
		5 17			5 0	9 45	Pulse 100, drops to 88
26	3	5 21¼	4 5	3 5	4 0	7 85	Pulse 86
30	2	5 27½	3 5	3 85	4 0	6 35	Pulse 84, patient somewhat restless
32	4 slowly	5 34½	2 5	2 6	5 0	8 4	Pulse 84, 1 c c per 10 sec Latent period for slow injections averages 15 sec, patient in good condition after treatment and much better than before, patient received 64 mg NaCN or 64 c c N/50 NaCN in 1 hr 15 min, Increase in pulse rate 146 per cent, latent period averages 23 sec

CASE 5—W H Y, man, aged 45, weight 120 pounds, treated June 16, 1917

Diagnosis—Dementia paralytica

After subcutaneous injections the stimulation was negligible, while only after large quantities intramuscularly was there any stimulation noted Intravenous injections produced stimulating effects as in other cases Increase in pulse rate 26 per cent Latent period twenty-three seconds

CASE 6—J H, man, aged 21, weight 125 pounds

Diagnosis—Dementia praecox

The patient was always extremely sluggish, made no effort to talk to anyone Was up and about every day State of nutrition poor

TABLE 5—CASE 6

June 19, 1917

No	Procedure N/50 NaCN, C c	Time	Respiration Before Rate	Respiration Before Vent	Respiration After Rate	Respiration After Vent	Remarks
5	2	9 22¾	5	5 6	5	5 9	Pulse 66
6	2	9 24	5	5 4	5	6 5	
7	2	9 25	5	5 1	5	5 7	
8	[illegible]	9 26½	5	5 7	5	8 1	
9	5	9 29½	5	4 8	5	8 7	Pulse 69
12	20 slowly	9 32½	5	4 2	5	7 8	1 c c in 10 to 14 sec
					6	11 7	Pulse 99, total 20 c c in 3½ min, slight flushing of face, no cyanosis See Figure 3
15	1	9 46¼	5	4 8	5	6 1	
16	2	9 47¼	5	6 5	5	7 4	
18	1	9 51½	5	4 7	5	5 6	
19	15 slowly	9 52¾	5	4 8	4	7 6	1 c c in 10 to 14 sec., face flushed
					5	7 9	1 c c in 10 to 20 sec, pulse 105, strong
					5	10 5	1 c c in 10 sec, total 15 c c in 5 min, skin moist
21	1	10 00¼	6	3 5	5	5 1	
22	1	10 01	5	5 1	yawn		
25	2	10 05	4	2 8	4	5 6	Pulse 90
26	2	10 06	4	5 6	3	5 8	

Results in the remainder of the treatment were similar to those recorded in the table Patient received in all 111 c c fiftieth-normal sodium cyanid in one hour and fifteen minutes Fifty-nine per cent increase in pulse rate Latent period twenty-one seconds

CASE 7—D G E, man, aged 25, weight 155 pounds

Diagnosis—Dementia praecox

Patient received 157 c c fiftieth-normal sodium cyanid, or 157 mg sodium cyanid in a period of one hour and fifty-eight minutes, patient in very good condition after treatment, no vertigo, pulse rose from 54 to a maximum of 87, latent period of stimulation of respiration twenty-two seconds

CASE 8—L C, man, aged 39, weight 100 pounds

Diagnosis—Dementia paralytica

For the previous eight months he had been confined to his bed

TABLE 6—CASE 8

June 21, 1917

No	Procedure N/50 NaCN, C c	Time	Respiration Before Rate	Respiration Before Vent	Respiration After Rate	Respiration After Vent	Remarks
3	2	10 20¾	6	10 2	5	7 8	
4	2	10 21	5	7 8	7	11 1	
5	1	10 22			6	9 2	
6	5 slowly	10 22¼	6	9 2	7	11 9	
8	5 slowly	10 25	6	7 4	7	12 5	
10	27 buret	10 31	6	7 6	8	17 5	Pulse 103, total 27 c c in 9 min
					7	10 8	1 c c in 27 sec
					7	14 5	1 c c in 14 sec
					9	17 4	
14	13 slowly	10 41	7	8 5	7	13 6	Total 13 c c in 6¼ min, pulse 103 at 10 41 a m
					8	16 7	Pulse 68 at 10 55 a m
26	2	11 05¼	7	11 3	7	16 9	
27	2	11 05¾	7	10 9	7	15 2	
28	16 slowly	11 06½	7	15 2	8	17 7	1 c c in 22 sec Total 16 c c in 5½ min, pulse 100 at 11 15 a m
33	2	11 19½	7	10 4	7	16 7	Pallor
34	2	11 21¼	6	13 0	8	15 5	
35	6 slowly	11 22½	7	13 7	8	18 7	1 c c in 18 sec, total 6 c c in 2½ min hiccough, pallor
39	3	11 35	8	19 2	8	22 0	Pallor Note Figure 4

Patient in good condition after treatment Patient received 93 c c fiftieth-normal sodium cyanid, or 93 mg in a period of one hour and twenty-two minutes Latent period twenty seconds

CASE 9—N J, man, aged 60, weight 140 pounds
Diagnosis—Dementia paralytica
Patient had been confined to bed for eighteen months

TABLE 7—CASE 9, TREATMENT 1

June 21, 1917 Buret injection

No	Procedure N/50 NaON, C c	Time	Respiration				Remarks
			Before		After		
			Rate	Vent	Rate	Vent	
9	5	2 05¾	11	8 4	11	11 6	
11	1	2 06¼					1 c c in 8 sec, no effect on respiration
12	2	2 07¼	12	8 4	12	12 7	
13	2	2 08½	11	6 4	11	12 9	2 c c in 10 sec
14	29 5 slowly	2 10	11	6 9	12	10 5	Pulse 91, 1 c c in 18 to 22 sec
					11	11 2	Pulse 102, face flushed
		2 20			12	16 8	Pulse 100, 1 c c in 25 sec, total of 29 5 c c in 10½ min
19	15 slowly	2 23	11	10 8	11	18 9	1 c c in 15 sec, face flushed Note Figure 5
					12	12 1	1 c c in 12 to 40 sec
					13	19 3	1 c c in 25 sec
					12	20 7	1 c c in 28 sec, pulse 100, total, 15 c c in 10 min
34	10 intramuscularly	2 57¾	13	12	13	11 7	Apparently no response
					13	12 5	

Patient received 65 c c fiftieth-normal sodium cyanid or 65 mg sodium cyanid in a period of one hour Increase in pulse rate 8 per cent, latent period twenty seconds

CASE 10—T Z, man, aged 21, weight 160 pounds Admitted to the hospital June 25, 1917, and had not spoken since admission, and therefore no history could be obtained Immediately following the injection he talked freely and gave a history which was later verified His mental condition was still improving

Diagnosis—Dementia praecox

TABLE 8—CASE 10

June 27, 1917 Buret injection

No	Procedure N/50 NaCN, C c	Time	Respiration				Remarks
			Before		After		
			Rate	Vent	Rate	Vent	
7	1	10 06¼	6	5 3			
8	1	10 06½			7	7 1	
9	1	10 07			6	5 8	
10	2	10 07½	6	5 8	7	7 8	
11	3	10 09	7	6 8	7	7 5	Pulse 74
12	5	10 10	7	6 8	8	12 1	
13	5	10 11¾	7	5 8	7	10 8	
14	2	10 13¾	7	7 0	7	8 7	Response to 2 c c, while there was little response to 3 c c before the 5 c c in Procedure 12
15	2	10 16½	7	5 6	7	7 8	Total 22 c c during this period
18	2	10 20¾	7	7 3	7	7 5	
19	5	10 21½	6	5 4	5	12 7	Apnea of 13 sec followed this stimulation
20	1	10 33½	6	4 7	7	6 5	Response here to 1 c c following 5 c c, while before this injection there was no response to 2 c c
21	2	10 24¾	7	6 1	7	7 0	
22	3	10 26	6	5 4	7	8 1	
23	3	10 27	6	5 5	6	8 0	Total 16 c c in 6¼ min
24	20 slowly	10 28	6	5 9	6	9 3	1 c c in 15 sec
					6	7 7	1 c c in 20 sec
					7	10 7	1 c c in 11 sec, pulse 108, face flushed total 20 c c in 4½ min
		10 35			8	7 6	Pulse 100
29	1	10 39½	7	5 7	6	6 0	
30	2	10 40¾	6	6 0	7	9 7	
31	2	10 42¼	7	6 5	7	10 0	Slight nausea (had 63 c c up to this time)
32	5	10 47¼	6	6 8	7	8 3	1 c c in 8 sec (5 c c in 1½ min)
34	2	10 49	7	5 6	7	8 3	2 c c in 5 sec
35	2	10 50	7	5 9	7	8 5	2 c c in 4 sec
36	2	10 51¼	7	5 7	7	8 4	2 c c in 11 sec
37	2	10 55	6	5 0	7	7 8	2 c c in 19 sec
38	1	10 55¼	7	5 8	7	6 8	1 c c in 4 sec
41	1	10 57	6	5 1	7	7 4	

TABLE 8—CASE 10—(*Continued*)

No	Procedure N/50 NaCN, C c	Time	Respiration				Remarks
			Before		After		
			Rate	Vent	Rate	Vent	
42	3	10 58¼	6	5 4	6	11 9	3 c c in 5 sec
43	3	11 00	6	5 0	6	10 8	3 c c in 10 sec
44	3	11 02	6	5 9	7	10 0	3 c c in 16 sec
45	3	11 03½	6	6 2	6	9 0	3 c c in 15 sec
46	3	11 06	6	5 7	7	8 8	3 c c in 18 sec
47	9	11 08½			8	9 5	1 c c in 12 to 16 sec, total 9 c c in 2 min, pulse 104, nausea, vomiting movements, pallor, pulse of good character
		11 10½					
50		11 15½			7	6 2	Pulse 70 Patient conversed all through latter part of injection It was the first time he had made any sort of statement since his admittance to the hospital

Patient received 102 c c fiftieth-normal sodium cyanid, or 102 mg in a period of one hour and four minutes He said he felt much better after the treatment Increase in pulse rate 32 per cent, latent period twenty-two seconds

DISCUSSION OF RESULTS

The protocols, together with the tracings, show clearly that sodium cyanid is a reliable stimulant to the respiration in every case in which we have administered it It should be noted that the graphic records of the respiration in our experiments do not show accurately the lung ventilation Thus, with a change in the type of respiration the bladder or bladders might less perfectly record the respiratory movements Frequently, following the administration of sodium cyanid, inspection of the chest clearly showed an enormous stimulation of the respiration, whereas the record shows but relatively slight stimulation Throughout, we may say that the records rather minimize the degree of respiratory stimulation

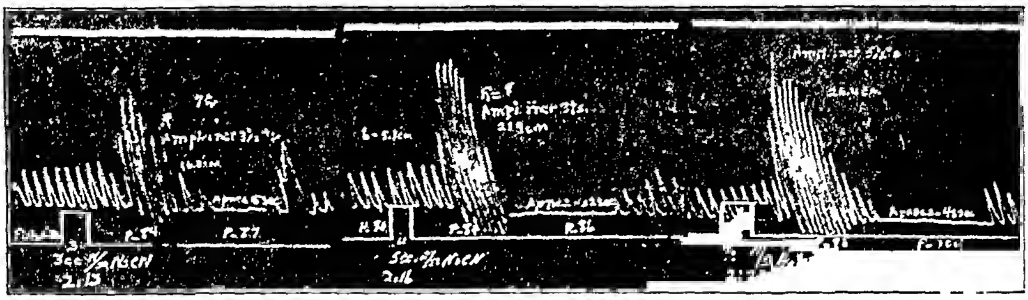
The therapeutic use of sodium cyanid in these cases has fully confirmed the results of the animal experiments, in that we have never had experience with any drug whose administration calls forth so exact a response in functional activity as is to be noted under the cyanid

The exactness of the control of the respiration under sodium cyanid is well illustrated in Cases 2 and 3 Records of the cyanid injections in these cases are shown in Figures 1 and 2 In Case 2, Treatment 1, as will be seen from the table, the stimulation of the respiration, both as to amplitude and rate, on rapid injection, is roughly proportional to the dosage In other cases the amplitude is markedly increased with

little or no change in the rate Figure 1 illustrates the type of respiratory stimulation which it would be most desirable to obtain in the resuscitation of drowning individuals The great respiratory movements as shown here following rapid injection of 5 c c fiftieth-normal sodium cyanid would be invaluable in expelling water from the lungs The respiratory pause shown in the record is apparently physiologic following the very active respiration and occasions no alarm

Figure 2 shows the remarkable control of the respiration under cyanid possibly even more strikingly The series of "beads" in the record, each representing a period of respiratory stimulation, could be produced at will

In regard to the margin of safety in the intravenous administration of sodium cyanid, we may say that in the fifteen therapeutic injections which we have made we have never experienced any alarming symptoms whatever either during the time of injection or at any time fol-



A B C

Fig 1 (Case 2) —Tracing illustrates the exactness of the control of the respiration under sodium cyanid, *A,* apnea of fifteen seconds followed stimulation, *B,* apnea of thirty-two seconds followed stimulation, *C,* apnea of forty seconds followed stimulation

lowing it On the other hand, we have seen in addition to the stimulation of the respiration observed during and immediately following the administration of the drug, a marked improvement in the general condition in many of these cases Thus, Case 2, Treatment 2, on June 11, was expected to end fatally during the early afternoon We were requested to administer the drug immediately as the respirations were extremely shallow Before the injection the temperature was 102 F , the pulse was 88, and the respirations 22 The injection was followed by a marked improvement in the general condition of the patient, and the following morning his temperature was 98 8 F , pulse 72 and respiration 20 Each of the four injections was followed by very obvious improvement in the general condition of the patient

The average latent period between the injection of the sodium cyanid and stimulation of the respiration in man was twenty seconds It is of interest to note that the latent period for any given case was constant on a single day, but varied on different days

The duration of stimulation from a single injection is almost proportional to the dosage and the rate of administration The duration of stimulation, however, following a single rapid injection of sodium cyanid rarely exceeds thirty seconds

The dosage required to give an outspoken stimulation of the respiration in man on rapid injection may be placed at from 3 to 5 c c of fiftieth-normal sodium cyanid

A single rapid initial injection of 1 or 2 c c of fiftieth-normal sodium cyanid which fails to elicit a stimulation of the respiration will often cause a perfectly obvious stimulation when given a certain period of time following the injection of larger amounts administered either slowly or rapidly

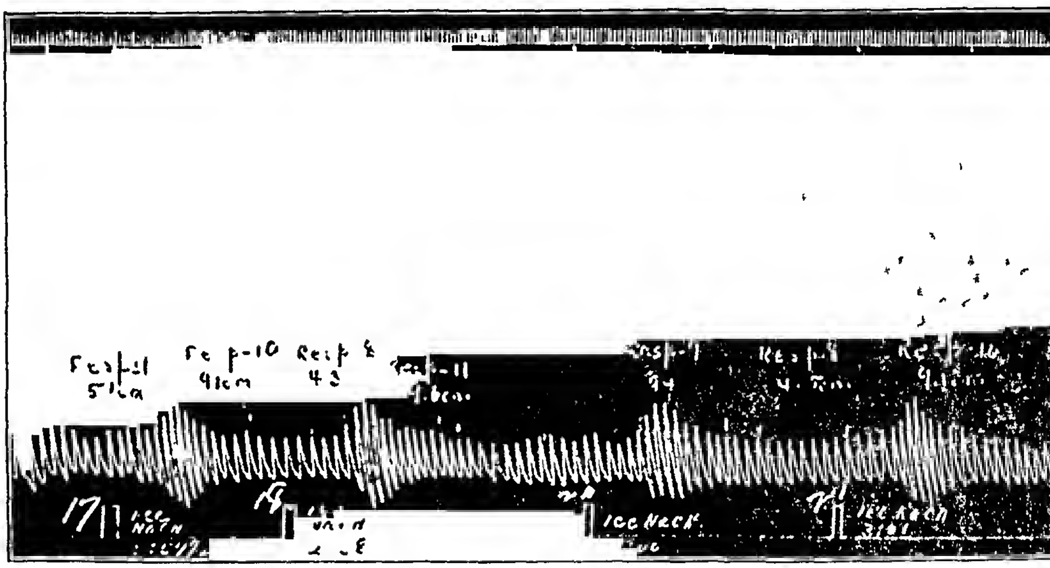


Fig 2 (Case 3) —Illustrating the effect on the respiration of sodium cyanid given 1 c c at a time

Our work throughout has confirmed the view that sodium cyanid is quickly transformed in the body to a nontoxic product It is difficult to give the rate of detoxification in the body, but it would seem that the human body can detoxify sodium cyanid when injected intravenously at the rate of 1 c c per thirty or forty seconds, because when injected at this rate over a considerable period of time the drug produces no effect whatever This offers the simplest explanation of the fact that doses which were insufficient to stimulate the respiration originally, may be efficacious when given a short time after other larger injections It is also possible that a previous injection may increase the irritability of the respiratory center toward cyanid, but we are inclined to believe that this is not the true explanation

Slow, continuous injections can be made by means of a syringe, although we obtained our most satisfactory results using the buret for such injections

The effect of intravenous injections of sodium cyanid on the circulation which we have noted are as follows

(*a*) Pulse rate We have noted that in most of our injections there is a tendency to an increase in pulse rate In some cases it was rather striking In Case 4, Injection 1, after the injection of 37 c c of sodium cyanid, the pulse rate rose suddenly from 52 to 128 After a very short time the pulse rate dropped to 84 This is the most extreme case of increase in pulse rate which we noted In other cases, the increase in pulse rate was much less, averaging 30 per cent

(*b*) Blood Pressure The blood pressure was taken by the auscultatory method in only one of our cases (Case 2, Injection 2) The variation of the blood pressure was well within the limit of error

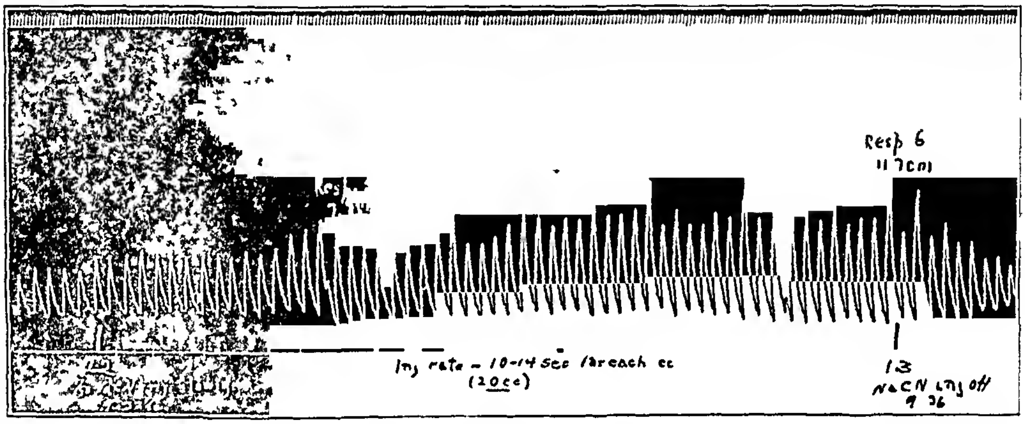


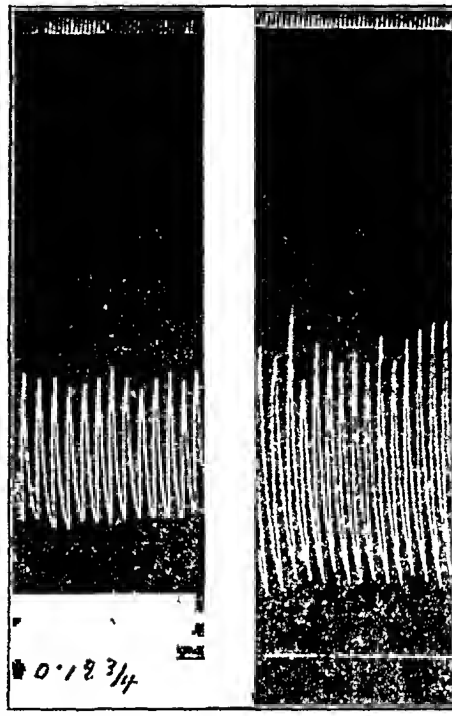
Fig 3 (Case 6) —Showing the effect of constant stimulation during the slow continuous injection of 20 c c fiftieth-normal sodium cyanid

(*c*) In certain of our cases in which there was a marked pallor of the skin before injection, we noted a general cutaneous hyperemia, in some instances with sweating In other cases, merely a flushing of the face was noted, and in still other cases a pallor developed during injection which may have been associated with a tendency to nausea

In Case 1, in which there was a serious heart lesion, no disagreeable symptoms of any kind were noted

Vomiting center In no case was actual vomiting produced by the injection of sodium cyanid One patient, Case 7, stated that he felt sick after a slow, continuous injection Another patient, Case 10, after an injection of 102 c c was nauseated, retching movements occurring At this time there was a pallor of the face The pulse was of good character

Evidences of stimulation of the cerebrum as a whole, especially the psychic centers, was obtained in a number of cases Thus, several patients, who had had their eyes closed for a long time, opened their eyes and looked about In two instances they yawned quite naturally



A B

Fig 4 (Case 8)—Effect of sodium cyanid on the respiration, *A*, normal tracing, *B*, shows stimulation eleven minutes after the injection of 6 c c fiftieth-normal sodium cyanid was completed

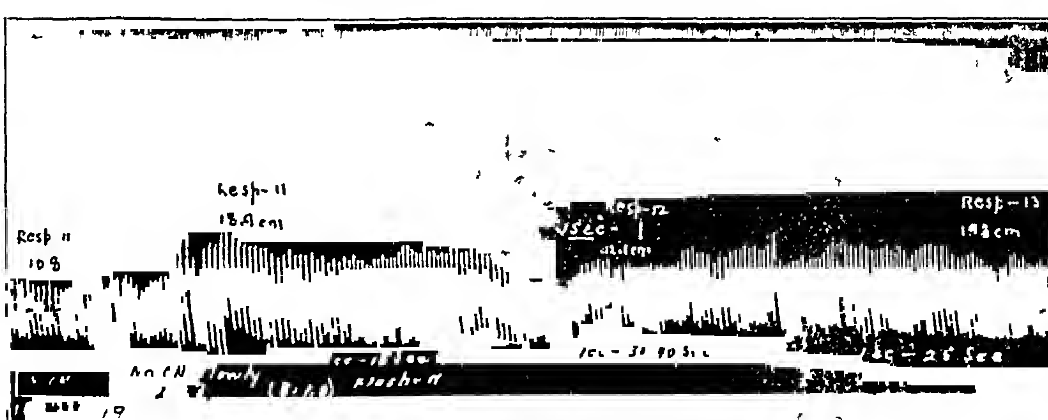


Fig 5 (Case 9)—Illustrating stimulation of the respiration during an injection of sodium cyanid in which the rate of injection was varied

as though they were awakening from a long sleep The most interesting instance of psychic stimulation was observed in Case 10 This patient, who had dementia praecox, entered the hospital June 27, 1917, and up to the time of the injection had not spoken a word, so that no history was obtainable except from the meager statements on his commitment papers After receiving an injection of 102 c c of fiftieth-normal sodium cyanid within a period of sixty-four minutes, the patient conversed, answered questions and attempted to explain his prolonged silence His history was then obtained for the first time We have, on the other hand, seen no evidences of motor stimulation Case 3 clearly indicates the absence of motor stimulation This man had been having one clonic convulsion after another for days, with occasional periods of rest During the injection, and for some time following it, the convulsions did not occur and the muscular twitching was much less marked In this case the cyanid seemed rather to depress than to stimulate the motor cortex

Attention has already been called to the fact that subcutaneous, perivascular, or intramuscular injection of fiftieth-normal sodium cyanid in man does not cause any local inflammatory reaction Therefore, from this point of view, the drug could be injected intramuscularly, but the dosage is not easy to determine when so administered and the delay in the therapeutic effect makes it impossible to gauge the dose nicely For the present, therefore, we do not recommend intramuscular administration of the cyanid

SUMMARY

The results of extensive animal experimentation, briefly summarized in the early part of this paper, necessitated a clinical investigation of the use of sodium cyanid as a respiratory stimulant Our clinical results may be briefly summarized as follows

1 We have treated ten patients with intravenous injections of fiftieth-normal sodium cyanid solution (0 1 per cent) The treatment was repeated in some cases so that in all, fifteen treatments were given In every case we have obtained a marked stimulation of the respiration on the average within twenty seconds after starting the injection The stimulation could be accurately controlled by the rate of injection The duration of the stimulation following a single injection depends on the dose and rate of injection It rarely exceeds thirty seconds The dosage required to produce therapeutic effects in man vary in different cases and according to the condition Thus, in the case of resuscitation from drowning, it may be desirable to give an adult an injection of 5 c c of fiftieth-normal sodium cyanid within a period of ten seconds This will give very large respiratory movements and should expel water from the lungs

2 In other cases showing great depression of the respiration, when it is desired to produce a milder and more continuous form of stimulation of the respiration, it is desirable to give a slow, continuous injection of fiftieth-normal sodium cyanid intravenously at a rate varying from 1 c c in thirty seconds to 1 c c in fifteen seconds, depending on the degree of stimulation and the condition of the patient Any competent observer watching the injection will have no difficulty in deciding the proper rate for a given case

3 The injection should either be slowed or temporarily stopped on the appearance of any of the following symptoms (1) marked pallor, (2) signs of nausea, (3) marked increase in the pulse rate, (4) depression of the respiration following too rapid injection or too large a dose, and (5) any other evident ontoward symptom should be the signal for stopping the injection

4 The factor of safety in the intravenous administration of fiftieth-normal sodium cyanid is sufficiently large for clinical purposes

5 It is our opinion that the intravenous injection of sodium cyanid may prove to be useful in the following conditions (1) depression of the respiration resulting from increased intracranial pressure however produced, until the condition can be relieved by decompression, (2) resuscitation from drowning, (3) embarrassment of the respiration under any form of anesthesia, and (4) other forms of respiratory depression, when it may be given in addition to artificial respiration Opportunity has not presented itself for us to study the effect of cyanid in all of these conditions

6 The effects of sodium cyanid injections on the circulation are not such as would detract from its clinical use

7 No disagreeable symptoms whatever developed as a result of the treatment in our clinical cases, and the condition of many of the patients was obviously improved In addition to the stimulation of the respiration, there is evidence of stimulation of other parts of the cerebrum, especially the psychic functions

8 It would seem superfluous to advise caution in the use of this drug We believe, however, that the method is a perfectly safe one in the hands of a cautious clinician [13]

13 Sodium cyanid tablets containing 100 mg may be obtained from Hynson, Westcott & Dunning, Charles and Franklin Streets, Baltimore One of these tablets, when dissolved in 100 c c of sterile physiologic salt solution, yields a solution suitable for this work In case the whole 100 c c is not used, it should be disposed of

THE INFLUENCE OF LARGE DOSES OF THYROID EXTRACT ON THE TOTAL METABOLISM AND HEART IN A CASE OF HEART-BLOCK *

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The effect of the ingestion of thyroid extract on normal and myxedematous people has been studied by several observers The general opinion seems to be that cases of myxedema and cretinism respond readily to thyroid extract by a considerable increase in basal metabolism, and that normal and obese people, while usually affected, respond to a less marked degree DuBois[1] reports a case of cretinism whose basal metabolism rose 20 per cent in three and one-half days under the influence of thyroid extract

The amounts of thyroid extract employed differ greatly in the investigations on normal and obese individuals A patient with obesity studied by Magnus-Levy[2] received the largest dose of thyroid extract that we know of — from 3 to 5 gm daily for nineteen days Anderson and Bergman[3] used large doses, but only for one day before observations Thiele and Nehring[4] used doses up to 0 9 gm a day

Observations vary as to the influence of thyroid on the total metabolism of normal and obese people Some investigators report an increase, others none Magnus-Levy[2] found a rise from 10 to 25 per cent following thyroid administration in three of five obese patients, and no rise in two Stuve[5] is reported to have found a rise in one patient after thyroid Anderson and Bergman,[3] after large doses the day before observation, found no rise in themselves except what they attributed to muscular exercise Thiele and Nehring[4] affirmed that thyroid tablets in all their cases caused a rise of gaseous metabolism

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* From the Medical Service and Respiration Laboratory, Massachusetts General Hospital

1 DuBois, E F Metabolism in Exophthalmic Goiter, The Archives Int Med, 1916, **17,** 915

2 Magnus-Levy Untersuchungen zur Schilddrusenfrage, Ztschr f klin Med, 1897, **33,** 269

3 Anderson and Bergman Einfluss der Schilddrusen Futterung auf dem Stoffwechsel des Gesundes Menschen, Skand Arch f Physiol, 1898, **8,** 326

4 Thiele and Nehring Untersuchungen des Respiratarischen Gaswechsel unter dem Einfluss von Thyreoideapparaten und bei Anaemischen Zustanden des Menschen, Ztschr f klin Med, 1896, **30,** 41

5 Stuve Festschr, Frankfort a M 1896, **44.**

Means[6] found an increase in one obese patient, but two showed no rise after the administration of thyroid for five days Jaquet and Svenson[7] found in some cases a rise in metabolism after thyroid, not in the basal observations, but in the extra energy given off following the ingestion of food Their observations vary markedly from day to day, however, and the amount of thyroid given is not clear

The present case is reported because of the marked effect of thyroid extract on the basal metabolism as well as on the auricular rate of the heart It was possible to study auricles and ventricles separately owing to the presence of complete auriculoventricular dissociation

REPORT OF CASE

History—C E A, woman, white, single, aged 24, violin teacher She had measles as a baby, and at 3 years scarlet fever and diphtheria simultaneously She had no other infectious diseases When 12 years old severe frontal headaches began which at first were biweekly, lasting from two to three days and associated with nausea, vomiting and abdominal pain There have been no attacks for eight years There has never been any syncope She has been nervous and easily excited, quickly tired and never strong She formerly felt cold all the time and had to wear extra clothes Her skin and hair have always been dry

Present Illness—Eight years prior to admission she felt increasingly tired Her arms began to ache, particularly the left, when worst, the pain occurred nightly and was so severe that she was kept awake and could not stand the pressure of the bed clothes The attacks continue though gradually less severe

For eight years she often noticed a sharp, severe pain in her left axilla, coming on after exertion At times she had to stop walking because of severity of the pain and inability to breathe About Nov 1, 1916, a very intense attack seized her, but she kept on walking in spite of it That night she could not move without pain

During the previous seven years her physicians have said her heart rate was slow, usually 50 Her mother said she had an irregular heart when 12 years old Seven years prior to admission her physician gave her thyroid extract without result This was done because her dry skin, sensations of cold and general condition offered the suggestion of myxedema Two years later she took 5 grains of thyroid every other day and improved, but she "usually got better in winter" In June, 1916, her physician, after consultation, decided to push the drug until symptoms appeared He increased the dose until she took for two weeks 26 or 27 grains of Burroughs, Wellcome & Co's thyroid tablets a day, and for the next three weeks 28 grains a day She said she had taken over 2,000 grains in from three to four months Nevertheless, she had no tachycardia, her pulse was never over 72 and seldom over 62 She had no headache, exophthalmos, diarrhea, loss of weight or sweating Her catamenia were normal, and sleep was good

In November, her physician called Dr Edsall in consultation, who suggested this investigation

Nov 6, 1916 Physical examination showed a quiet, well developed and nourished girl Her hands revealed a slight tremor Her thyroid gland was

6 Means, J H Studies of the Basal Metabolism in Obesity and Pituitary Disease, Jour Med Research, 1915, **32** (new series 27), 121, The Basal Metabolism in Obesity, The Archives Int Med, 1916, **17**, 704

7 Jaquet and Svenson Zur Kentniss des Stoffwechsel Fettsuchtigen Individuen, Ztschr f klin Med, 1900, **41**, 375

not palpable Her heart apex by percussion was 10 5 cm to the left of the midline The beat was forceful and the second sound sharp There was a rather loud blowing systolic murmur everywhere The heart was slow and block was suspected The skin of her hands was soft and silky, her hair dry and fine Her face was sallow and slightly coarse Her eyes were not prominent The basal metabolism was determined Thyroid administration, 28 grains a day, was continued

November 13 The hands were slightly swollen The electrocardiograph confirmed the diagnosis of heart block The basal metabolism was determined Blood sugar 0 081 per cent Thyroid continued

November 16 Thyroid extract was omitted

November 18 No thyroid was given on the third day The basal metabolism was determined Polygram (Fig 1), electrocardiogram and roentgenogram were taken

Roentgenographic report Seven foot plate of the heart The apex is 8 cm to the left of the median line, right border is 5 3 cm to right of the median line, total transverse diameter, 13 3 cm , greatest transverse diameter of great vessels, 6 5 cm , length of heart, 15 2 cm , diameter at base, 10 4 cm , enlargement of heart to the right Prominence of auricle

November 20 Basal metabolism determined Blood sugar 0 09 per cent

November 21 Wassermann test negative

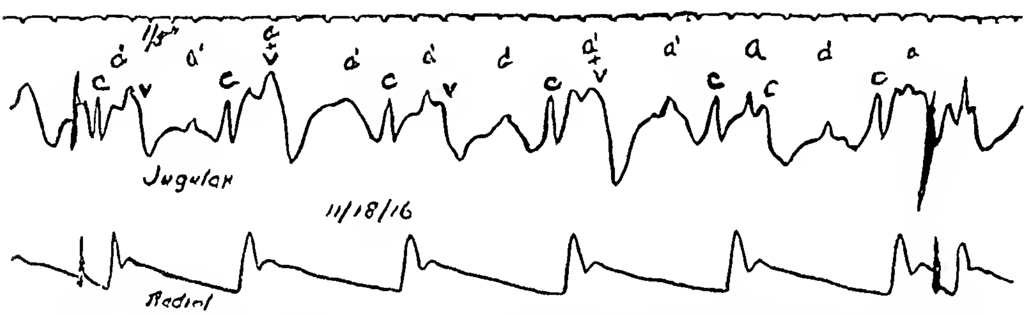

Fig 1—Polygram taken Nov 18, 1916 Complete auriculoventricular dissociation Auricular rate 108 per minute, ventricular rate 51 per minute

December 4 No thyroid for nineteen days She gets overtired now, cannot sleep, and feels cold all the time Basal metabolism determined, and electrocardiogram taken (Fig 2)

December 7 An attack of precordial pain, which radiated to her left arm, lasted several hours

December 17 No thyroid for thirty-two days Her skin is somewhat drier than before Metabolism determined

December 23 Electrocardiogram and polygram taken

Jan 27, 1917 Admitted to the Massachusetts General Hospital Discharged February 4 Eight days prior to admission on climbing the stairs after one and one-half hours of violin practice, her heart began to beat forcibly, with an occasional strong beat, which her physician said was an extrasystole This condition lasted a few days This afternoon her left arm aches severely and she feels very tired

Physical Examination—The pupils were dilated but reacted normally, the heart apex was seen and felt in the fourth space 14 cm to the left of midline and 3 cm beyond the nipple, right border of dulness 2 cm to right, her feet were cold, there was no tremor of the hands The chart showed a range of pulse between 51 and 64 Urine and feces were normal, white count of blood, 16,700, differential count was normal

January 28 The basal metabolism was determined No thyroid in seventy-four days

January 31 Electrocardiograms were taken before and after subcutaneous injection of one-fiftieth grain of atropin sulphate (Fig 3)

February 1 Electrocardiograms were taken before and during right and left vagal and right ocular pressure, and immediately after walking 220 yards

DISCUSSION

The basal metabolism determinations (Table 1) were made with the Benedict unit apparatus [8] The patient was fasting at least fourteen hours and was at complete rest for at least one-half hour before, as well as during all observations Every observation was checked by two observers

The dose of thyroid ingested by the patient had been gradually increased by her physician until from 26 to 27 grains were taken daily for two weeks, and 28 grains a day for three weeks before she was seen by us and for ten days thereafter She had thus taken about 1,000 grains in the course of five weeks, and over 2,000 grains in from 3 to 4 months

As a result of these large doses, her average total basal metabolism was 54 5 and 52 3 calories per square meter per hour These figures show a marked increase, 47 and 41 per cent, respectively, over the standard of 37 calories per square meter per hour found for a normal woman of her age However, there were no other symptoms of hyperthyroidism than this increased metabolism and the increased auricular rate There was no sweating, no nervousness, no diarrhea or exophthalmos There was no loss of weight On the contrary, she even claimed to have gained slightly

After the omission of the thyroid the return to normal metabolism was very rapid For sixty hours the metabolism continued at the same high level as before, namely, +40 per cent But within the next forty-eight hours the metabolism dropped to +28 per cent One week later, on the twelfth day after the omission of the drug, the metabolism had fallen to +11 per cent, a point practically within normal limits Another week brought the variation to but 3 per cent above normal

As the height of the metabolism diminished the weight of the body increased, the net gain from November 13 to December 17 being 3 7 kg, about 8 pounds

The respiratory quotients as obtained by the unit apparatus are not very accurate, and no great emphasis can be laid on them Normally, they vary with a change in the percentage of foodstuffs burned In this case they give no indication of a marked changed in the percentage of fat and carbohydrate utilized during and following thyroid ingestion

Furthermore, there was no appreciable effect on the blood sugar by the thyroid medication November 13, while thyroid was still being

8 Benedict, F G Ein Universalrespirationsapparat, Deutsch Arch f klin Med, 1912, **107**, 156

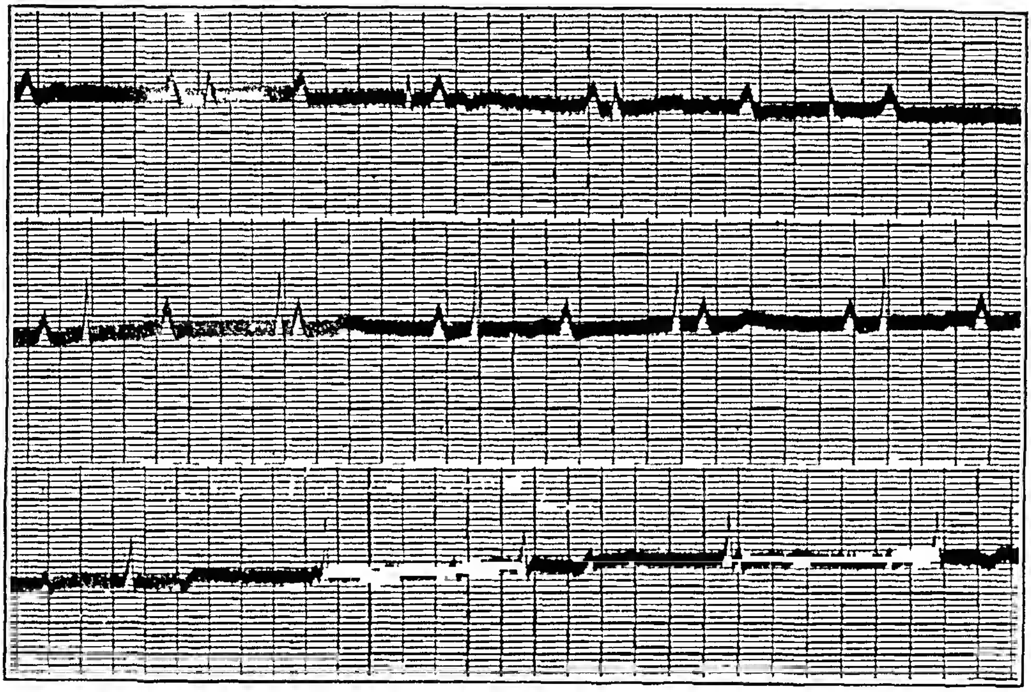

Fig 2—Electrocardiogram (Lead II), Dec 4, 1916 Complete auriculoventricular dissociation, average auricular rate 71, average ventricular rate 50

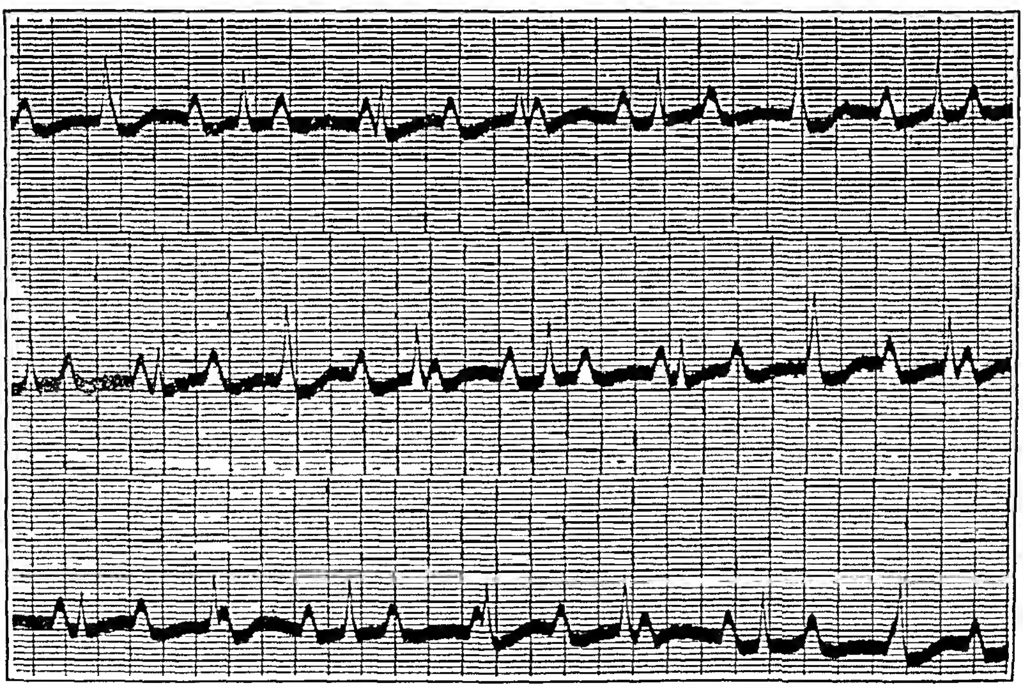

Fig 3—Electrocardiogram (Lead II), Jan 31, 1917 Forty minutes after the subcutaneous injection of one-fiftieth grain of atropin sulphate Auricular rates upper record 116, middle record 135, lower record 120, average ventricular rate 74

TABLE 1.—METABOLISM DATA

Girl aged 24 years. Height, 157 cm. Normal Metabolism, 37 calories per square meter per hour

Date	Average Pulse	Weight, Kg	Surface Area Height and Weight Chart	CO_2 per Minute, C c	O_2 per Minute, C c	Respiratory Quotient	Average Total Calories per Hour	Average Calories per Square Meter per Hour	Variation from Normal Standard, per Cent	Thyroid Administration
11/6/16	57 60 56			229 223 227	285 295 285					
Average	58	53.0	1.52	226	288	0.80	82.9	51.5	+17	28 grains a day
11/13/16	55 55			229 236	269 279					
Average	55	54.0	1.53	233	271	0.85	80.0	52.3	+41	Still taking 28 grains a day
11/18/16	55 54			212 216	276 281					
Average	55	54.8	1.54	214	278	0.77	79.6	51.7	+40	Thyroid stopped after November 15. No thyroid the third day
11/20/16	54 53			218 226	241 218					
Average	54	53.5	1.53	222	241.5	0.91	72.7	47.3	+28	No thyroid the fifth day
11/27/16	56 53			192 192	215 216					
Average	55	55.5	1.55	192	216	0.89	63.7	41.1	+11	No thyroid the twelfth day
12/4/16	52 52			168 165	203 205					
Average	52	55.5	1.55	167	204	0.82	59.2	38.2	+ 3	No thyroid the nineteenth day
12/17/16	49 48			185 189	224 236					
Average	49	57.7	1.57	187	230	0.81	66.4	42.3	+14	No thyroid the thirty second day
1/28/17	64 61			175 170	221 217					

administered, the blood sugar was 0 081 per cent, and November 20, five days after omission of the drug, the blood sugar was 0 090 per cent, both normal figures

From the cardiac point of view the case is one of the few of complete auriculoventricular dissociation in which the ventricular rate is 50 or over Several cases in the literature show a high ventricular rate when the dissociation was due to digitalis poisoning, but only a few in which the cause of the block was organic Lea,[9] Hunt,[10]

TABLE 2—Electrocardiographic Rates

		Average Auricular Rate	Average Ventricular Rate	Remarks
11/13/16		119	57	Thyroid 28 grains a day
11/18/16		102	58	No thyroid for 3 days
11/20/16		100	57	No thyroid for 5 days
12/ 4/16		71	50	No thyroid for 19 days
12/23/16		75	55	No thyroid for 38 days
1/31/17	103* 96 110	103	65	Before atropin
1/31/17	116 135 120	124	74	After atropin, gr 1/50
2/ 1/17		75	56	Normal
2/ 1/17		75	56	During right vagal pressure
2/ 1/17		75	56	During left vagal pressure
2/ 1/17		75	55	During right ocular pressure
2/ 1/17		73	55	Immediately after walking 220 yards

* Auricular rates before and after atropin, as determined by the electrocardiograph

TABLE 3—Polygraphic Rates

11/18/16	108	51
12/23/16	77	49
1/28/17	70	50

Windle,[11] Neuhoff[12] all report cases of complete auriculoventricular dissociation in which the ventricles beat at a rate of from 50 to 60 per minute, and even higher under certain circumstances

The present case showed variations in pulse rate from 48 to 64 at the times of the metabolism studies The electrocardiograph showed

9 Lea, Edgar Complete Heart-Block with Higher Ventricular Than Auricular Rate, Lancet, London, 1915, **1**, 1289
10 Hunt, G H Exhibition of Clinical Case, Lancet, London, 1913, **1**, 1312
11 Windle, J D Permanent Complete Heart-Block, Heart, 1910, **2**, 102
12 Neuhoff, S Complete Heart-Block with Rapid, Irregular Ventricular Activity, Am Jour Med Sc, 1913, **145**, 513

variations in the ventricular rate from 50 to 65, and forty minutes after the subcutaneous injection of one-fiftieth grain atropin sulphate, an increase to 74

The auricles, when the patient was still under the influence of thyroid, beat at the rate of 119 November 18, three days after thyroid was omitted, the auricular rate had fallen to 102, two days later to 100, and by December 4, the nineteenth day after stopping the thyroid, to the normal rate of 71 Thereafter the auricular rate was constantly about 75, except on January 31, when for some unexplained reason — perhaps excitement — it rose to an average of 103 at the same time as the ventricular rate rose to 65 The next day the auricles beat regularly at 75

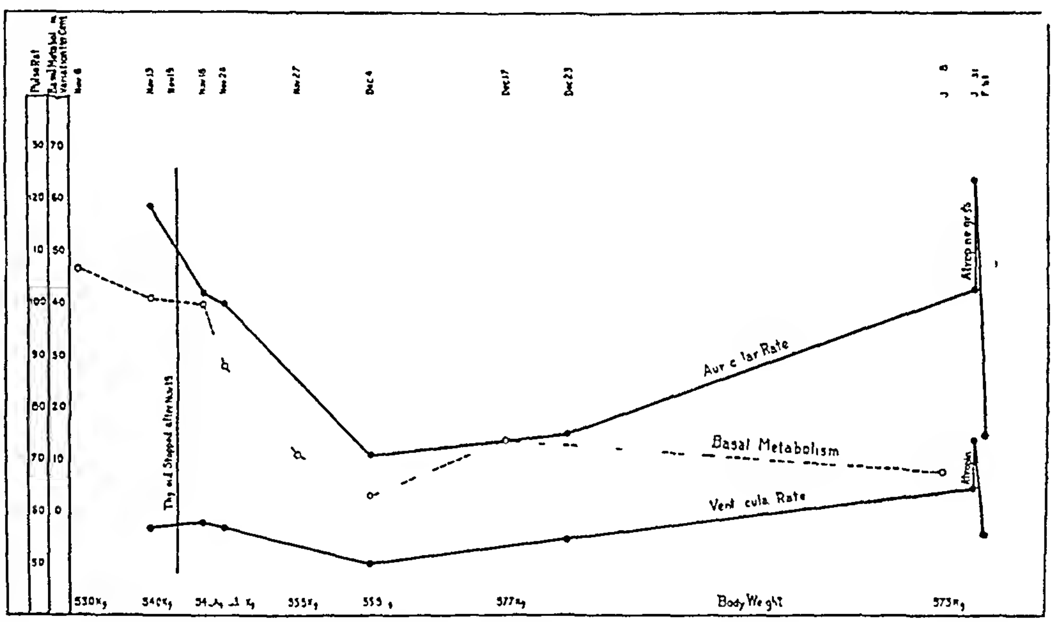

Fig 4—The influence of large doses of thyroid extract on the total metabolism and heart in a case of heart block

The auricular rate curve and the metabolism curve (Fig 4), though drawn to different scale, show a parallelism that is worthy of note

The fact that the auricular rate was definitely modified by the ingestion of thyroid to give an auricular tachycardia, while the ventricular rate was in no wise influenced, seems to indicate that thyroid substance produces tachycardia through nervous channels and not by direct action on the muscle

The subcutaneous injection of one-fiftieth grain atropin sulphate affected the rate of both auricle and ventricle The auricles beat at the high rate of 135 (average 124) instead of at the previous high rate of 110 (average 103), an increase of about 23 per cent (average 20 per cent) The ventricular rate rose from 65 to 74, an increase of about

14 per cent According to Frédéricq,[13] this latter indicates that the heart-block is not absolute, that some vagus fibers, whose terminal filaments were paralyzed by the atropin, had been exerting an inhibitory action on the ventricles Other mechanisms, however, are conceivable by which the phenomenon might be explained

Right and left vagal pressure, right ocular pressure, and exercise produced no effect on either auricles or ventricles

SUMMARY

A case of complete auriculoventricular dissociation is reported for the following reasons

1 Thyroid extract was administered in increasing doses so that by the end of a period of from three to four months over 2,000 grains had been ingested For the last four weeks of this period the dose amounted to 28 grains a day The only effects observed from taking these large amounts of thyroid were an increase in the basal metabolism of 47 per cent above normal and a rapid auricular rate of 120 After the withdrawal of the thyroid the basal metabolism fell to normal limits within twelve days and the auricular rate within nineteen days (perhaps less) During the first months after the thyroid was omitted the body weight increased over 8 pounds

The thyroid administration had no apparent effect on the respiratory quotient or the blood sugar

2 The auricular rate was influenced by thyroid extract, but not the ventricular, which suggests that thyroid does not increase the heart beat by direct action on the muscle, but through nervous channels

We wish to express our thanks to Dr Edsall for permission to make these studies of his patient and for his constant stimulating interest, and to Drs J H Means and P D White for valuable aid and suggestions

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13 Fredericq, Henri Critique de l'emploi des eprouves de l'atropine et du nitrite d'amyle dans le diagnostic des bradycardies, Arch d mal du coeur, Par, 1916, **9**, 377

EXTENSIVE CALCIFICATION OF THE LUNGS AS A DISTINCT DISEASE*

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Calcareous deposits, especially local, are of frequent occurrence in degenerated and necrotic tissue, old inflammatory exudates, and other dead material such as thrombi Calcification in the media and intima of the arteries in old persons, in pleural and pericardial exudates where large calcareous plates may form, the concretions in the apices of the lungs and in the bronchial lymph nodes as the result of tuberculosis, are all familiar examples Wherever tissue degenerates, deposits of calcium salts may take place, usually in the stroma, but also, although rarely, in the cells themselves, as, for instance, in the renal epithelium in toxic necrosis, in ganglion cells, in muscle fibers Deposition of calcium salts also occurs on a larger scale, when it may give rise to peculiar conditions and even distinct diseases The cause of such deposits is in general assumed to be a supersaturation, so to speak, of the blood and tissue fluids with calcium salts If the normal elimination of calcium by way of the intestinal tract and the kidneys is disturbed as, for instance, on account of nephritis, calcareous deposits occur more readily Added to this we have the facts that certain organs and tissues are predisposed to calcareous infiltration, namely, the lungs, the endocardium of the left ventricle, the pulmonary veins, the gastro-intestinal mucous membrane and the kidneys, as shown in 1885 by Virchow, who described calcareous infiltrations of these organs in diseases of bones in the course of which calcium salts are set free, more particularly in bone tumors, either primary or secondary, but also in osteomalacia and in leukemic conditions Virchow called this process lime or calcium metastasis It is believed that a lowered acidity of the blood in these organs and tissues may account for their predisposition to calcific deposits According to Wells,[1] some thirty-six cases of extensive, and, as a rule, multiple, calcareous "metastasis" had been described up to 1915, since then some additional cases have been reported Still different are the cases in which deposition of lime salts takes place primarily in certain tissues or organs in persons who do

* Submitted for publication Sept 3, 1917

1 Wells, H G Classification and Ossification, THE ARCHIVES INT MED, 1911, **7**, 721 Metastatic Calcification, Ibid, 1915, **15**, 514 These articles contain references to the literature

not appear to suffer from any other disease except such peculiar deposits A form of this condition is infiltration of calcium salts in bursae, tendon sheaths, etc, which may occur as an independent process and cause more or less severe disturbances of function A number of cases of this kind have been described recently in Norway by Paus and Natvig (subacromial bursa), and by Sinding-Larson and Kjerschow (subepichondal bursa) In these cases there was found in the bursae white, chalky masses or a milky fluid with smaller, hard concretions and incrustation of the surrounding tissues, the masses consisting principally of carbonates and phosphates of calcium In the tissues were chronic inflammatory changes with indefinite giant cells, enclosing small calcareous masses, but no demonstrable primary necrosis, on the inner wall of the bursae were small papillomatous outgrowths A rare but also more serious condition is "calcinosis universalis," cases of which have been described recently, which is a chronic affection, especially of young persons, sometimes of several children of the same family, but also of older persons Phosphates and carbonates of calcium are deposited as nodular or band-like formations, or as softer, crumbling or even confluent material, especially in the subcutaneous tissue as well as in bursae, tendons, muscles, about nerves, and often in symmetrical form As a rule the internal organs are not involved and the joints and bones appear to be normal Over affected parts the skin may be pigmented and hard Various vasomotor changes have been observed The upper as well as the lower extremities and also the trunk may be affected Muscular atrophy takes place and invalidism in different grades results External irritation, injury or rheumatic attacks may hasten the depositions, which also may take place in paroxysms with fever, swelling, redness and tenderness of the parts involved As a rule, however, the process is gradual If a softening takes place, with secondary infection, death may result from septicopyemia There appears to be no primary degeneration in the connective tissue or elastic elements, which are especially affected, and it seems reasonable to assume that it concerns a metabolic anomaly of an unknown nature

The following case under the care of Dr Winge is an illustration

A woman, 63 years old, suffered many years until the hands and fingers became greatly deformed and enlarged on account of extensive deposits around all the joints, there was a fluctuating swelling on one buttock as large as half a hen's egg, which on incision was found to contain a liquid and semisolid, clumpy, white material, extending along the subcutaneous tissue through fascia and muscles clear to the bone, so that it was not possible to make a complete removal A clump 4 5 by 7 5 cm, white as chalk and irregular, was removed and found to contain carbonate, phosphate and a little oxalate of calcium

Morbid infiltration with calcium salts without evident cause may take place also in internal organs, and I have examined a remarkable

case of most extensive calcareous deposition in the lungs, which it is my special purpose to report

History—The patient was a woman, 41 years old, a workingman's wife, admitted to the service of Prof P F Holst, Feb 10, 1917 The family history was good, no children While a child and also three years prior to admission, she had acute rheumatism, the last attack being rather mild, for some time she had had dyspeptic symptoms, pain in the region of the stomach, and during the previous three years several rather large hemorrhages from the stomach, occasionally she would have severe nose bleed, and once it was very extensive, menstrual bleeding was also severe During the previous ten years she would get out of breath easily, and recently dyspnea would come on readily at the same time that the face seemed to become blue In the summer and fall of

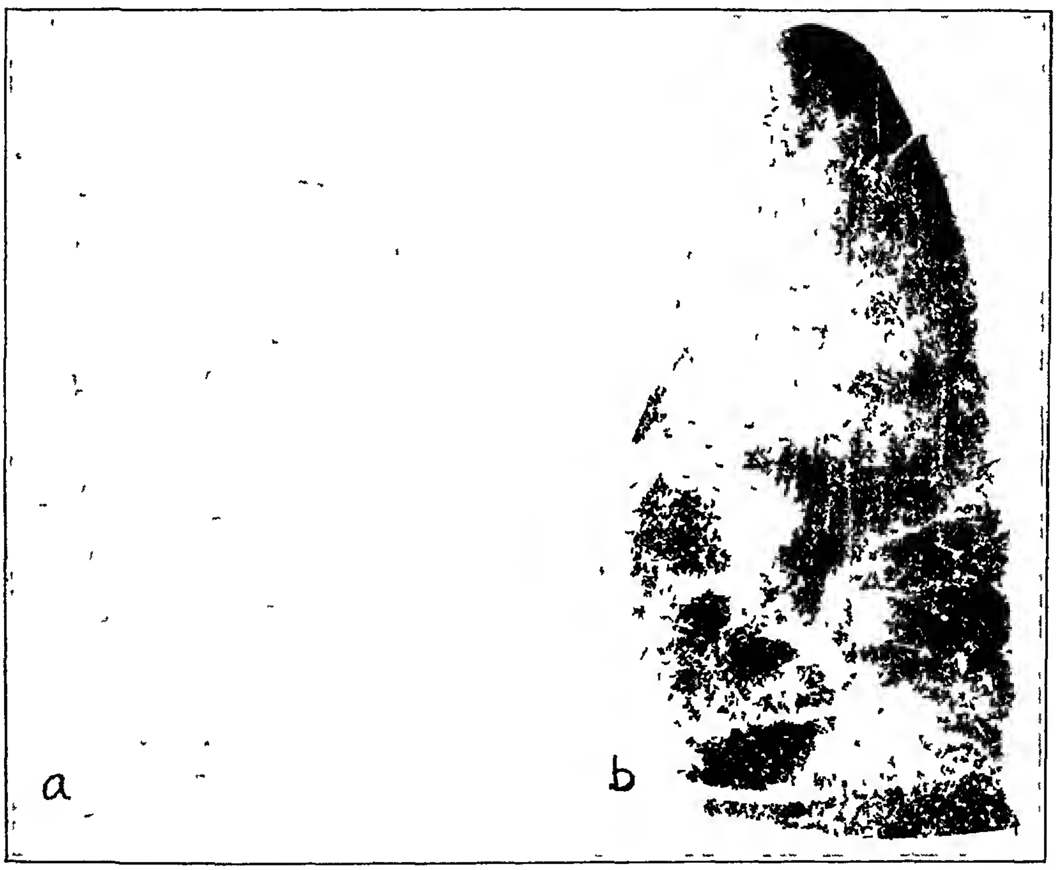

Fig 1—Roentgenograms of sections of the same thickness of normal lung (*a*) and calcified lung (*b*)

1916 the legs became edematous, at Christmas time the edema returned, and at the same time the abdomen became large, the urine small in amount and deeply colored, and from then on dyspnea forced her to sit up in bed at night

Examination—On admission the face was cyanotic, there was anasarca, the finger tips were club-shaped, pulse 104, respirations 34, prolonged expiration, especially over the left lung, at the base of the lungs, fine crepitation, heart somewhat enlarged, especially to the right, loud systolic murmur, most marked at the apex, with accentuation of the second pulmonary sound, blood pressure 110, liver enlarged, ascites, urine of specific gravity of 1 032, no albumin, blood or sugar

A few days later the blood showed 8,448,000 red corpuscles and 11,600 leukocytes

Under treatment with digitalis and theobromin sodium salicylate the edema diminished and the urine increased in amount, but before long the edema again increased, also the cyanosis, the heart action became irregular, and the patient died suddenly, March 3

Necropsy—The postmortem showed cyanosis and edema of the legs The heart was enlarged, weighing 400 gm, the enlargement involving practically exclusively the right side, the heart muscle was normal, valves normal, and the coronary arteries only a little sclerotic and not narrow, the aorta was normal, without calcareous deposits

There was no fluid in the pleural cavities, a few fibrous bands were present over the left lung and general adhesions over the right, the lungs were large, as in croupous pneumonia, solid and heavy, feeling like stones and sinking in water, the right lung weighed 2,750 gm, the left 2,130, in all 4,880 gm Placed on the base, the lungs stood by themselves, in consistency the substance was almost like wood, but not uniformly so, being apparently full of small, solid particles, and under the pleura here and there were small, white, flat masses of mineral nature The substance could be cut only with difficulty and felt like porous bone Passing the finger over the surface felt like rubbing it over sandpaper, and here and there were round or irregular concretions The distribution of mineral matter was about the same in both lungs, perhaps a little more marked in the left The cut surface was peculiar, reddish-brown, with numerous small holes in an extensive stroma, bloody, frothy fluid exuded, The first impression that the lungs were free of air and compact was not correct, air was present everywhere, but the air-containing tissue was less in amount than the interstitial tissue with the mineral deposits Areas in the anterior border of the right lung and the anterior surface of the upper lobe contained more air than other parts of the lungs After drying a small slice of lung substance it had a peculiar yellow red color and a porous surface which felt like sandpaper and from which small calcareous granules would fall out In both apices, at the hilus of the lungs and in the lymph nodes in the neck, were small, old caseous foci The pulmonary arteries were sclerotic but not calcified or dilated, the pulmonary veins were normal No calcification was present in the larger bronchi, trachea, or larynx

Mouth, pharynx and esophagus were normal

The thyroid gland was rather large, weight 29 gm, parathyroid glands not enlarged, no traces of the thymus

The peritoneal cavity contained 900 c c clear yellow fluid, lining smooth

Spleen, liver and kidneys were passively congested

Microscopic Examination—Microscopically there were no changes in the kidneys, except that the glomeruli were quite cellular and that under the capsule were occasional linear infiltrations of round cells

In the surface of the left adrenal was a small concretion

The ovaries were small and fibrous, tubes tuberculous, containing caseous material and tubercles in the mucosa

No ulcers or definite scars were found in the stomach, the mucosa of which was normal under the microscope

The hypophysis, which was large and weighed 1 1 gm, appeared normal on microscopic section

The spinal column, ribs, femur, sternum and cranial bones were normal so far as could be determined on careful gross and microscopic examination

Frozen sections of the lungs showed numerous round and oval concretions in the interstitial tissue, and compression of the alveoli In decalcified section the concretions have a lamellated structure, concentric, there being no needle shaped crystals or larger masses, the clumps lie in the interalveolar tissue and encroach on the alveolar spaces (Fig 2) The stroma is increased in amount, in places sclerotic, also anthracotic and infiltrated with round cells The veins and capillaries in the septa are dilated and there are hemorrhagic infiltrations

into the septa as well as into alveoli and small bronchi In places the alveoli appear as narrow clefts, in other places as small spaces with swollen desquamated cells, and then again as large spaces, the lungs being not totally solid anywhere The larger vessels and the bronchi appear normal There were no signs anywhere of old diffuse inflammatory processes, such as chronic bronchitis or pneumonia On addition of sulphuric acid to frozen sections, typical gypsum crystals formed, of hydrochloric acid, gas bubbles Chemical analysis (H Siebke) gave 78 05 per cent ash, of which 18 3 per cent consisted of calcium carbonate and about 80 per cent of calcium phosphate, as well as small quantities of iron, magnesium, etc

The extensive lime deposits in the lung in this case, so extensive that it seems quite remarkable that life lasted as long as it did, do not appear to be duplicated by any reports in the literature either of genuine "metastatic" deposits or of the few cases in which there was no definite cause It is noteworthy that the lungs weighed nearly six times as

Fig 2—Photomicrograph of decalcified section of calcareous lung between the large alveolar spaces numerous round, concentrically constructed calcareous clumps are seen

much as normal and that on first impression they appeared to be almost entirely airless, the deposits were diffuse and evenly distributed throughout the lungs, showing that they were independent of local changes such as thrombi or infarcts

For purposes of comparison I wish to mention briefly certain cases of calcification of the lung which I have found in the literature These may be devided into two groups, (1) the metastatic, dependent on bone destruction, and (2) cases like the one I have described in which there were no indications of bone disease

1 In addition to a number of cases of metastatic calcification, some of moderate degree only, described by Virchow, Kockel, Askanazy and others, I would mention especially the following cases The case described by Tschistowisch and Kollesnikoff of extensive calcium

metastases in the lungs and other organs associated with multiple myeloma, the lungs were large, very heavy, hard, dry, the surface grayish-white and rough, due to deposits in the walls of the alveoli and around the blood vessels Pari's case in a patient who died from cancer of the uterus with bone metastases, in which there was general calcification of the lungs, the surface was coarsely porous, dry, grayish-white and rough, there being also present larger, more completely calcified areas And in the instance described by Wells, who mentions the cases just cited, of extensive calcification in the heart and lungs in a case of myologenous leukemia, the lungs were heavy, solid and felt sandy

In this group probably belongs the following case, the facts in regard to which I obtained through the courtesy of Professor Quensel in Upsala and Dr Hellman

The patient was a woman, 65 years old, who died with symptoms of intestinal obstruction and marasmus The lungs were enlarged, grayish-red and looked as if powdered, on removal they retained their form, were solid and heavy but floated in water, finger depressions remained The cut surface seemed as if dusted with fine sand and a grayish-red frothy fluid could be pressed out The heart, kidneys, liver and spleen seemed normal The mucous membrane of the stomach was dark red and showed numerous small depressions surrounded by narrow, less deeply colored elevations, but whether this was due to calcification was not determined The intestines were normal, there was coprostasis The cranium was normal in form and thickness but very soft, consisting mostly of diploe, and both the surfaces showed irregular dark-red and grayish-white spots The brain and its membranes were normal

There was here a diffuse and extensive calcification of the lungs and possibly also of the stomach, due most likely to a primary disease of the bone, as indicated by the appearance of the cranium, but the exact nature of this disease we do not know

As examples of the second group, I would mention the case in which Virchow found grayish-white incrusted nodes as large as nuts in one lobe in a woman, 43 years old, with chronic pleuritis and nephritis, but no disease of the bones, Chiari's case in a woman, 27 years old, with gastric ulcer and general marasmus, half of the right lung being hard, grayish-white, grating on section, microscopically, there were calcareous deposits in the wall of the alveoli and in the vessels, there were also a few calcareous foci in the left lung and calcification in both kidneys, bones normal Hlava also found calcification in spongy form, of the right upper lobe, especially, in a person who died with circulatory disturbances Kockel described microscopic calcification in the lungs in a number of cases in some of which there was heart disease, while Kischensky found advanced calcification in part of one lung in a woman with chronic nephritis, amyloid disease, but with no changes in the bones Here belongs also the case described by Stade, who found an extensive deposit of calcium salts in the lungs of a man,

44 years old, who died with pneumonia and who had no changes in the bone system The substance of the lung was rough like sandpaper, solid, and microscopically the calcification was extensive

We see that in no case of either group was there so extensive and complete a calcification of the lungs as in the one I have described Usually the calcification seems to have been rather limited, sometimes strictly local, but there are cases in which it was diffuse, as, for example, in the case described by Virchow as follows "Lungs mostly grayish-white, resistant, especially at the borders of the lobules, calcified, cut surface porous like a sponge, with small holes, dry, rough, alveoli everywhere, large and wide" The cases described by Pari, Stade and Wells are also characterized by extensive deposits

In regard to the cause of calcification in the lungs, it appears that in most cases it may be regarded as metastatic in Virchow's sense, that is, as secondary to some form of destructive bone disease, with solution of the calcium salts in the bone and secondary deposition in other tissues In some cases the evidence of bone destruction is not definite In a small group, however, there is not the slightest evidence of any bone destruction, this would seem to be especially true in my case, in which several bones were carefully examined with this point in view In my case the kidneys were also normal, so that there is no reason to believe that there was any interference with calcium elimination by way of the urine Neither were there any extensive changes in the stomach or intestines, the most important places of calcium elimination, so that we are without any indications that in this case diminished calcium excretion was the reason of the calcification in the lungs The question arises whether there were peculiar degenerative or dystrophic conditions in the lungs which would induce precipitation of calcium salt, as is believed is the fact in necrotic and degenerated tissue In this case such changes would have had to be diffuse, and there is no evidence that such changes were present The dyspnea and cyanosis, which were noticed for many years, may have been the result of the calcification, possibly calcification might result from chronic stasis and secondary nutritive changes in the walls of the alveoli, but there is no way to account for any primary stasis in this case, as the condition of the heart clearly was secondary and there was no sign of previous disease in the lung, such as interstitial pneumonia, on the basis of which calcification might have taken place The possibility that some organ with internal secretion was at fault must be considered — the parathyroid glands, the thyroid, the hypophysis, the thymus, and the ovaries There is evidence that the parathyroid glands influence calcium metabolism; removal of these glands increases elimination of calcium and disturbances of ossification In osteomalacia, rickets and senile osteo-

porosis, tumors and other changes have been found in the parathyroid glands In my case, however, there were no changes in the parathyroids, the thyroid, thymus, or hypophysis Whether any significance is to be placed on the fibrous condition of the ovaries in this case is indeed a question We know but little of the influence of the ovaries in calcium metabolism The ovaries are frequently fibrous in young women in whom there are no demonstrable disturbances of calcium elimination or metabolism Taking it all in all, there are in this case no changes in the internal organs to explain the calcification in the lung It would seem, then, that one is driven to assume that in such cases as I have described there is a "constitutional anomaly" or metabolic disturbance of unknown nature, in consequence of which calcium salts are deposited from the blood in apparently normal tissues, and especially in the lungs, perhaps on account of the low acidity of the blood as it gives up carbon dioxid

AURICULAR FLUTTER *

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Sixteen cases of auricular flutter have been observed in the Mayo Clinic by us during the last thirty months In the study of these cases a review of the literature revealed certain features which made it seem desirable to record our findings The paucity of case reports in the literature is ample evidence that the condition is frequently overlooked

Definition—Auricular flutter may be described as an acceleration of the auricles to a rate beyond 200 per minute [1] In all reported cases such acceleration has been accompanied by a partial heart block, giving a ventricular rate of one-half, one-third or one-fourth of the auricular rate, or a total dissociation of rhythm (complete heart block), or the degree of block may vary between the auricular beats, giving a gross ventricular arrhythmia The partial block is apparently due to the inability of the auriculoventricular bundle to conduct impulses so rapidly, or to the inability of the ventricle to respond so rapidly There is no reason to suppose that organic disease exists in the bundle except in those few cases (two, one our own, reported to date[2]), in which there is evident complete dissociation, and in a small group of ventricular bradycardias in which the auriculoventricular bundle may at least be questioned In the paroxysmal attacks, when the ventricles assume the full auricular rate, we have evidence of a temporary increase in irritability of the ventricle or the auriculoventricular bundle

There is no known pathologic difference between an auricular rate of less than 200 and one at which the rate exceeds this figure, yet the clinical manifestations are so different as to justify the classification of flutter as a clinical entity [3] The fundamental clinical differences

* Submitted for publication Sept 20, 1917

1 Hertz, A F, and Goodhart, G W The Speed-Limit of the Human Heart Quart Jour Med, 1908-1909, **2,** 213

2 Jolly, W A and Ritchie, W T Auricular Flutter and Fibrillation Heart, 1910-1911, **2,** 177

3 Lewis, T Observations on a Curious and Not Uncommon Form of Extreme Acceleration of the Auricle "Auricular Flutter" Heart, 1912-1913, **4,** 171

lie in the fact that flutter tends to persist indefinitely, whereas auricular paroxysmal tachycardia rarely reaches so rapid a rate and the attack stops after a relatively short period In flutter the auricles continue their rapid rate when the ventricles are slower, while in auricular paroxysmal tachycardia 1-1 rhythm is always present and the sinus rhythm is restored between attacks

Experimental—Auricular flutter was produced experimentally by MacWilliam in 1887[4] by mild faradization of the auricles of exposed animal hearts Lewis (1912-1913) observed the same condition after the intravenous injection of glyoxylic acid[5] Hirshfelder[6] (1908) produced it by ligation of the coronary arteries, and similar observations have been made after cooling the auricles and during chloroform anesthesia In our laboratories, working with Kendall, we produced, experimentally, hyperthyroidization in the goat by a large injection of the thyroid active principle, alpha-iodin[7] We have observed auricular flutter as one of the cardiac phenomena shown by practically continuous electrocardiographic tracings over several hours preceding death

Mechanism—Flutter is caused by focus of stimuli in the wall of the auricular muscle at a point outside the normal pacemaker or sinus node (ectopic stimuli), the discharge of stimuli being at a rate so rapid and continuous as to submerge the sinus activity This conclusion is based on the fact that the P wave is found to have an abnormal form in the clinical electrocardiogram and that in the experimental study the P wave approaches the normal contour as the stimulus is applied nearer the sinus node

A statement of methods by which flutter can be produced in the laboratory will help to visualize the subject A single shock applied with the stimulating electrode to any point in the wall of the auricle causes an auricular extrasystole, providing the stimulus is applied when the muscle is not contracting A continued mild faradization applied to the same point causes similar contractions, but each contraction is maximal, and hence only when the muscle begins to relax, or pass out of the "refractory phase," is further stimulation effective, then another contraction is caused by succeeding stimulus, etc In

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4 McWilliam, J A Fibrillar Contraction of the Heart Jour Physiol, 1887, **8**, 296

5 Lewis, T The Mechanism of the Heart Beat with Special Reference to the Clinical Pathology London, Shaw, 1911, p 311

6 Hirschfelder, A D Contributions to the Study of Auricular Fibrillation, Paroxysmal Tachycardia, and the so-called Auriculo-(atrio) Ventricular Extrasystoles Bull Johns Hopkins Hosp, 1908, **19**, 322

7 Kendall, E C The Isolation in Crystalline Form of the Compound Containing Iodin which occurs in the Thyroid, its Chemical Nature and Physiological Activity Tr Assn Am Phys, 1915, **30**, 420

other words, the auricle is contracting as rapidly as possible—a state of "flutter" during the time continuous faradization is applied

Thus, if asphyxia is allowed to act, a visible change is found in auricular activity Suddenly the auricle dilates and ceases coordinate contraction, but each little individual muscle bundle begins to contract regardless of the muscle mass, that is, incoordinated contraction In other words, multiple foci of irritability occur throughout the auricular mass due to asphyxiation The dilated auricle as a whole is functionless It acts only as a reservoir, but close inspection reveals the fibril-

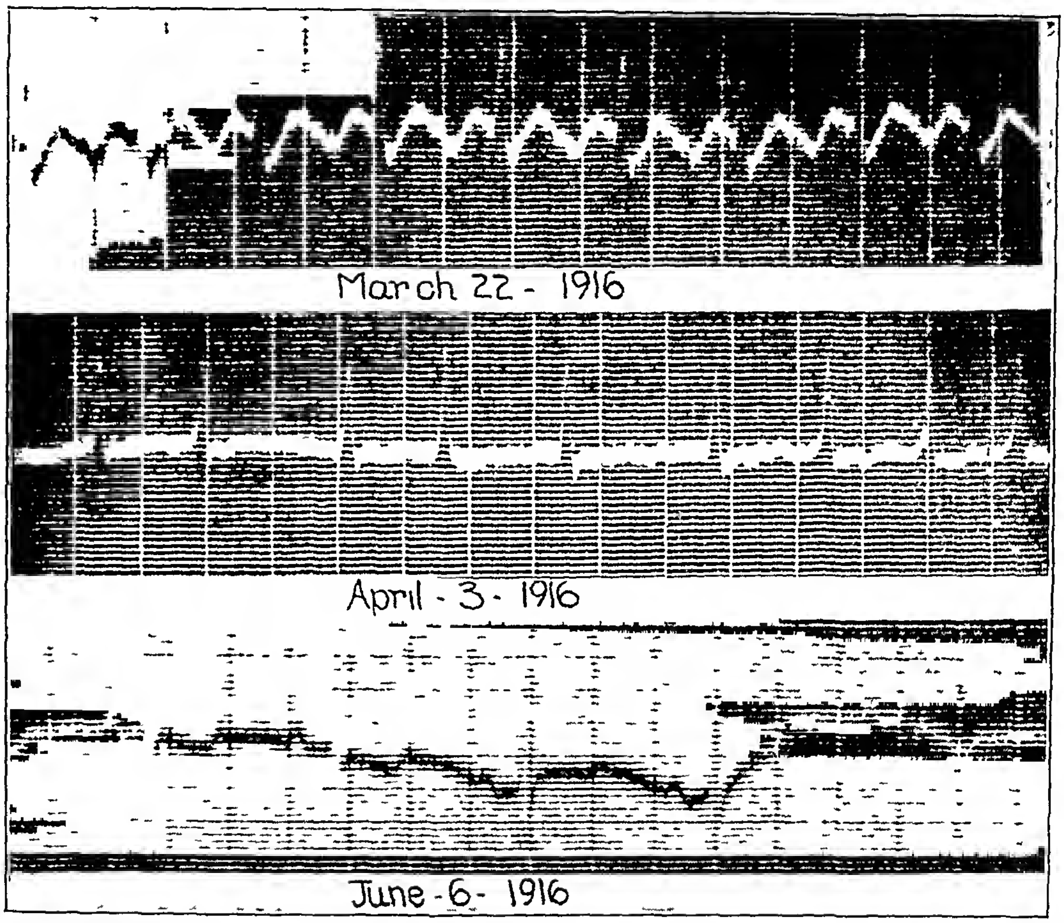

Fig 1 (146153) —1 Typical auricular flutter 2 Fibrillation induced by digitalis 3 Normal rhythm following thyroidectomy

lating muscle twitching which is characteristic of auricular fibrillation, and the total arrhythmia of the ventricular action is at once apparent

In the human heart the irritable focus causing flutter must be the result of disease It cannot be too strongly emphasized that flutter, per se, is only objective evidence of localized irritability in the auricular wall, and that any other organic cardiac disease may exist in the same heart

It is evident that at present no clear distinction, mechanical or organic, can be given as differentiating paroxysmal auricular tachycar-

dia from auricular flutter The difference is largely a well-grounded clinical conception based on a different symptomatology The only objective distinction is one of auricular rate, and that a partial block usually exists in flutter cases

Pathology—It is already evident that auricular flutter is not a pathologic entity, for we often see auricular extrasystoles, flutter fibrillation and a sinus rhythm in a single case within a relatively short time The literature contains only six necropsy reports in unquestioned cases, our series contains two others Ritchie[8] has reported a lymphocytic infiltration of the epicardium, most marked in the region of the sinus node, and he thinks this may have depressed sinus activity The cases of Gulland and Mackenzie,[9] and Hume's[10] first case add nothing significant to these findings The pathologic findings are at present unimportant, since so little has been recorded

The irritable auricular focus is the essential feature, and our study must include all causes of localized injury or irritability to heart muscle Such causes may be classified under three heads (1) infections causing localized injury, (2) general and local myocardial degeneration from any cause, as hypertension, valvular disease, goiter, etc , and (3) localized malnutrition of the auricular wall as in coronary sclerosis, etc

We do not know why in certain cases a localized injury should be selected from more extensive myocardial damage to become a source of irritation, and to send forth such rapid impulses as to submerge the sinus rate and establish flutter That such functional pathology exists, however, is evident

We have no evidence that flutter can be purely of neurogenic origin In all the reported cases and in our own cases there was either objective evidence of other cardiac damage or a history indicating infectious, toxic, myocardial or coronary etiology

Etiology—Auricular flutter occurs four times as often in men as in women, counting the reported cases and our own The average age of the patients was 47 years, the youngest 6 years and the oldest 82 years The condition is most frequent between the ages of 40 and 60 years, but in our series more cases[7] occurred between 30 and 40 years of age

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8 Ritchie, W T Further Observations on Auricular Flutter Quart Jour Med, 1913-1914, **7,** 1

9 Mackenzie, J Diseases of the Heart Ed 3, London, 1913, p 105

10 Hume, W E A Polygraphic Study of Four Cases of Diphtheria with a Pathological Examination of Three Cases Heart, 1913, 1914, **5,** 25.

Our cases at once call attention to an etiology of infection, since antecedent diseases of probable streptococcic origin were noted with remarkable frequency, namely, 1 rheumatic fever, 5 tonsillitis, 6 bad teeth, 6 "grippe," 2 pneumonia In 3 cases the patient dated his symptoms from one of these infections All the patients in our series gave histories of one or more of the foregoing diseases In 59 reported cases there is little data on this phase of the subject, but when given, the streptococcus group predominates, thirteen histories of rheumatic fever are recorded[11] Venereal disease plays no evident part

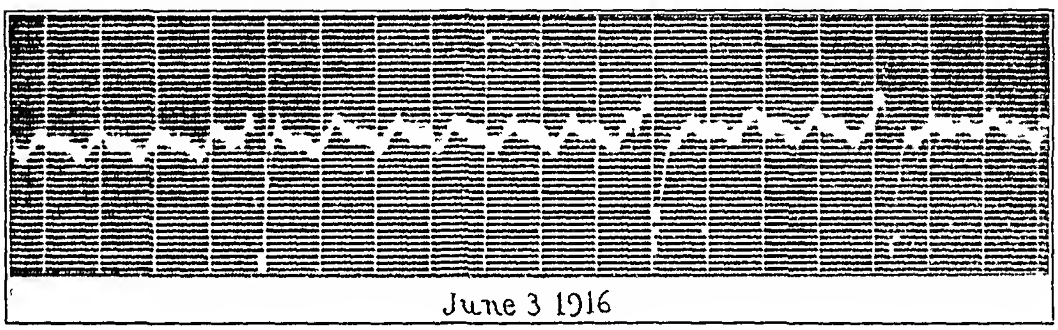

Fig 2 (161186) —Auricular flutter with heart block, auricular rate 260, ventricular rate 43

None of our patients was syphilitic, though three cases are noted in the literature[12] We noted four histories of typhoid fever, other reports contained one case[13]

Exophthalmic goiter was definite in four of our cases and was believed to be the probable etiologic factor One other such case is reported[14] Mitral disease was observed in but one of our sixteen

11 Mathewson, G D A Case of Auricular Flutter Edinburgh Med Jour, 1913, **11,** 500 Ritchie, W T Further Observations on Auricular Flutter Quart Jour Med, 1913-1914, **7,** 1 Gunson, E B Auricular Flutter Followed by Paroxysmal Auricular Fibrillation Lancet, London, 1914, **2,** 151 Levine, S A, and Frothingham, Jr, C A Study of a Case of Auricular Flutter The Archives Int Med, 1915, **16,** 818 Neuhof, S Auricular Flutter Accompanying Acute Endopericarditis Med Rec, New York, 1915, **88,** 995 Tallman, M H Auricular Flutter Northwest Med, 1916, **15,** 145 Sutherland, G A Auricular Flutter in Acute Rheumatic Carditis Brit Jour Child Dis, 1914, **11,** 337 Ritchie, W T Auricular Flutter Edinburgh, Green, 1914, p 33 Mackenzie, J Diseases of the Heart Ed 3, London, 1913 Appendix, Cases 68 and 69 Quoted by Ritchie, Footnote 14

12 Gunson, E B Auricular Flutter Followed by Paroxysmal Auricular Fibrillation Lancet, London, 1914, **2,** 151 Ritchie, W T Auricular Flutter Edinburgh, Green, 1914, p 33 Cowan, J Diseases of the Heart London, Arnold, 1914, p 205

13 Tallman, M H Auricular Flutter Northwest Med, 1916, **15,** 145

14 Ritchie, W T Auricular Flutter Edinburgh, Green, 1914, p 33 Sutherland, G A Auricular Flutter in Acute Rheumatic Carditis Brit Jour Child Dis, 1914, **11,** 337

patients, though the literature[15, 2] reports ten cases of stenotic or double mitral lesions

Relative Incidence—We examined electrocardiographically 3,500 patients and observed 16 auricular flutter records There were 363 patients with auricular fibrillation, 160 showing auricular extrasystoles, 316 showing ventricular extrasystoles and 5 auricular paroxysmal tachycardia These figures are doubtless far from a fair average, because we examined a great number of patients suffering from toxic goiter (both hyperplastic and nonhyperplastic) and fibrillation is very common in such cases The proportion of 16 flutters to 363 fibrillations is probably a fair average

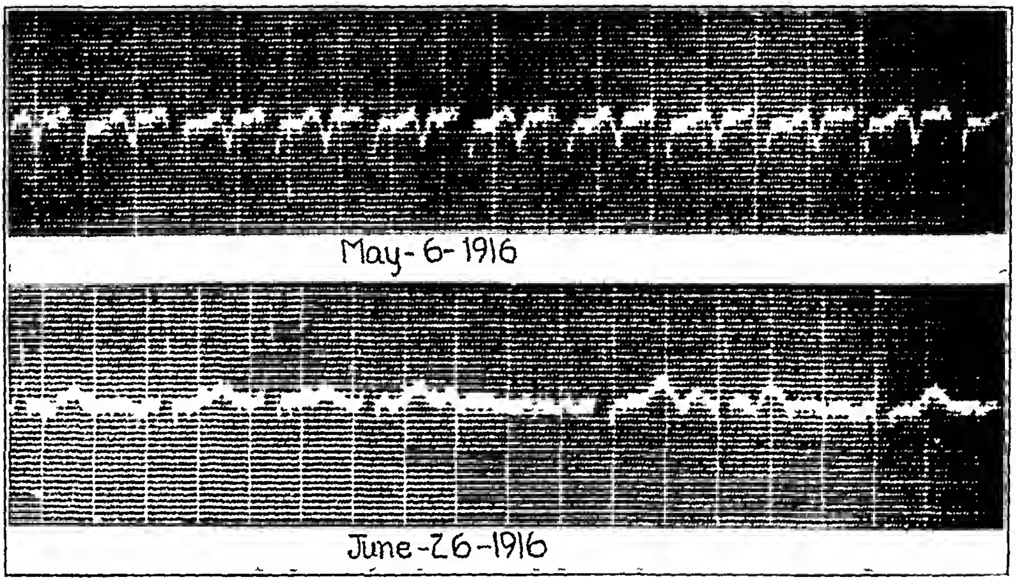

Fig 3 (158953)—1 2-1 flutter, auricular rate 316, ventricular rate 158 2 Fibrillation induced by digitalis

Symptoms—The symptoms of the condition depend essentially on the ventricular rate and the cardiac compensation The symptoms do not depend on the auricular rate alone, for the auricles may be found at 320 and the patient may not be aware of serious trouble, or the auricles may be dilated and functionally inactive (fibrillation) yet with good cardiac compensation and with little or no discomfort Symptoms are further confused by disease to which the flutter is incidental or terminal, as in mitral disease, arteriosclerosis or chronic nephritis In

15 Lewis, T Observations on a Curious and Not Uncommon Form of Extreme Acceleration of the Auricle "Auricular Flutter" Heart, 1912-1913, **4,** 171 Mackenzie, J Diseases of the Heart Ed 3, London, 1913, p 105 Ritchie, W T Auricular Flutter Edinburgh, Green, 1914, p 33 Rihl, J Klinische Beobachtungen uber atrioventriculare Automatie mit Bradykardie Ztschr f exper Path u Therap, 1911, **9,** 496 Gibson, G A A Discussion on Some Aspects of Heart Block Brit Med Jour, 1906, **2,** 1113

such cases flutter is clearly a manifestation of serious nutritional disturbance in the auricular wall and should be regarded only as a symptom worthy of relief

Flutter cases may be conveniently classified as paroxysmal or chronic depending on the duration of the disorder We use the term "paroxysmal" in cases in which the normal rhythm is restored between attacks lasting a few hours or days and "chronic" when the condition tends to persist

Paroxysmal flutter is not clearly defined from auricular paroxysmal tachycardia, as before mentioned We have observed it only as a disorder incidental to evident myocardial disease, it is serious because of the great strain on the myocardium Short paroxysms of flutter occur in which the auricular rate is between 200 and 380 and the ven-

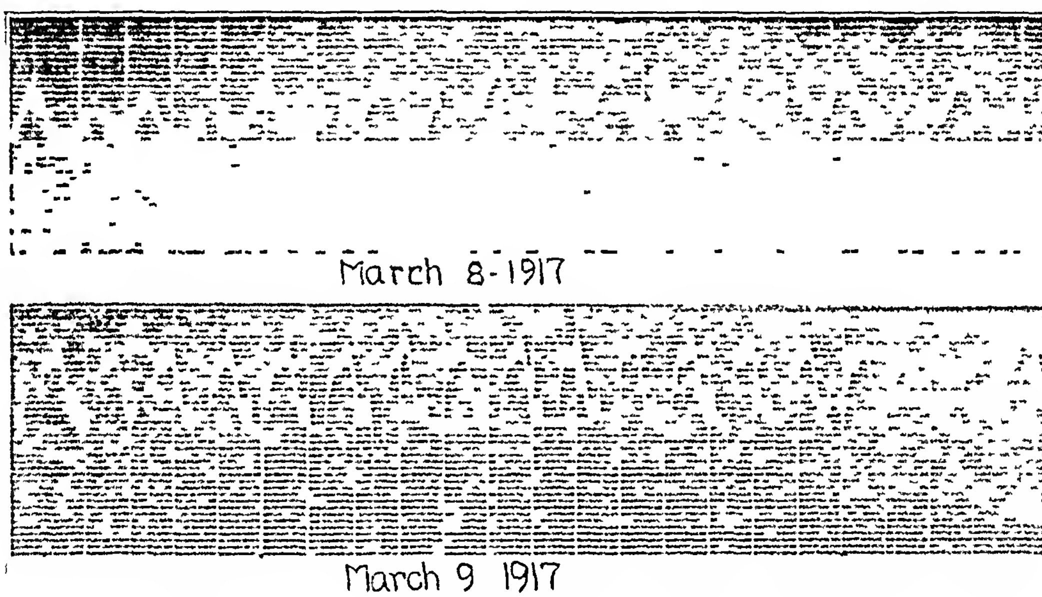

Fig 4 (187575) —1 2-1 flutter; auricular rate 224, ventricular rate 112 2 Paroxysm of 1-1 flutter, rate 232

tricular rate bears a definite or indefinite ratio to the auricular The attack gives symptoms of cardiac embarrassment varying in degree with the cardiac compensation and the length of the attack Palpitation, tachycardia, flushing, breathlessness, weakness, flatulence, pallor, vertigo, polyuria, faintness and syncope come on as the attack progresses, though sudden relief may come at any time from cessation of the attack We have seen, alternately, attacks of flutter and fibrillation in the same patient

Chronic flutter should always be recognized, for it can usually be relieved The flutter lasts for long periods, for weeks or even years, and can be detected by proper tracings at any time during its course The ordinary auriculoventricular ratio is 2-1 and the pulse is usually

100 to 180, but any degree of block may exist The pulse, therefore, may vary from idioventricular rhythm, 32, to the full auricular rate, 320

The most constant symptoms in our cases have been persistent and obscure tachycaria and weakness Most of the patients are subject to "weak spells"—violent paroxysmal attacks of tachycardia with acute cardiac insufficiency brought on usually by exertion and by stopping suddenly In such paroxysms the ventricles assume or approximate the auricular rate Certain patients have described it as "a feeling like a bird fluttering in the chest," which is probably a fairly characteristic sensation An occasional patient is very little inconvenienced by the paroxysm and in such instances the trouble is most likely to be overlooked

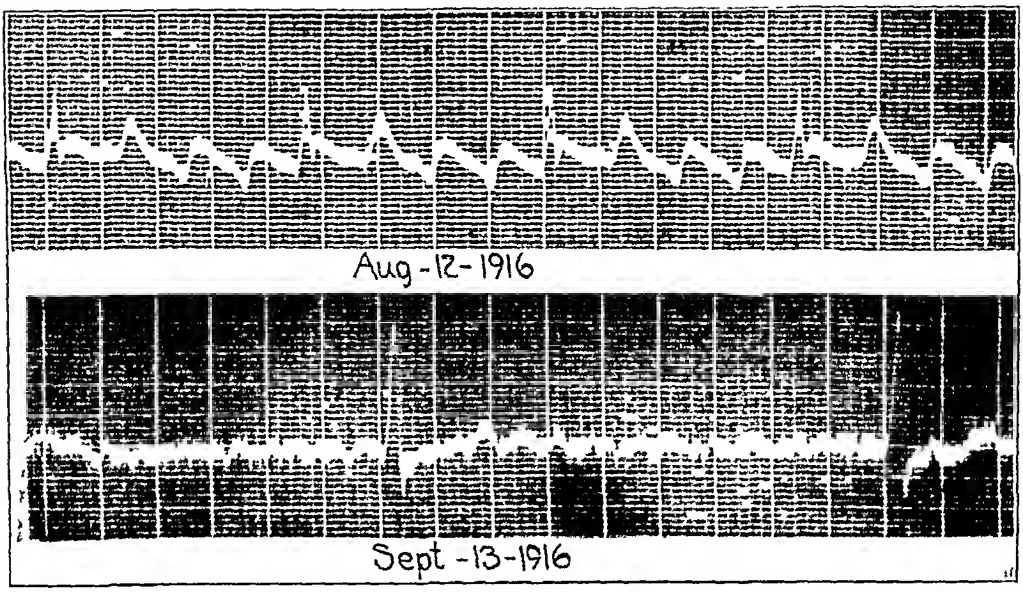

Fig 5 (168507)—1 4-1 flutter 2 Fibrillation with complete heart block under digitalis

Objectively, the heart may be normal except for weak sounds and a tick-tack rhythm Usually there is a tachycardia more or less marked, and often there is mitral stenosis In one half of our cases the pulse has been regular and in the others markedly irregular, owing to regular or irregular conduction through the auriculoventricular bundle Rapid, regular venous pulsation in the neck is indicative of the disorder, and any patient more than 30 years of age with a tachycardia unaccounted for, and particularly if he is subject to "weak spells," should be under suspicion

Vagal Pressure—In certain cases vagal pressure will promptly reduce the ventricular rate by increasing the degree of block, but the auricular rate is not affected by this procedure, contrasting sharply

with the cases of auricular tachycardia in which sinus rhythm is suddenly restored by vagal pressure The slowing of the ventricle is but transitory, and is recognized as due to increasing the degree of block temporarily by causing vagal depression of the auriculoventricular bundle

The diagnosis rests finally on graphic tracings, and we believe the electrocardiograph to be far the most satisfactory While we disclaim expert knowledge of the polygraph, we feel sure that the findings with this instrument may easily be misinterpreted and are not invariably conclusive

SUMMARY OF CASES

Following is a brief summary emphasizing the interesting features in our cases

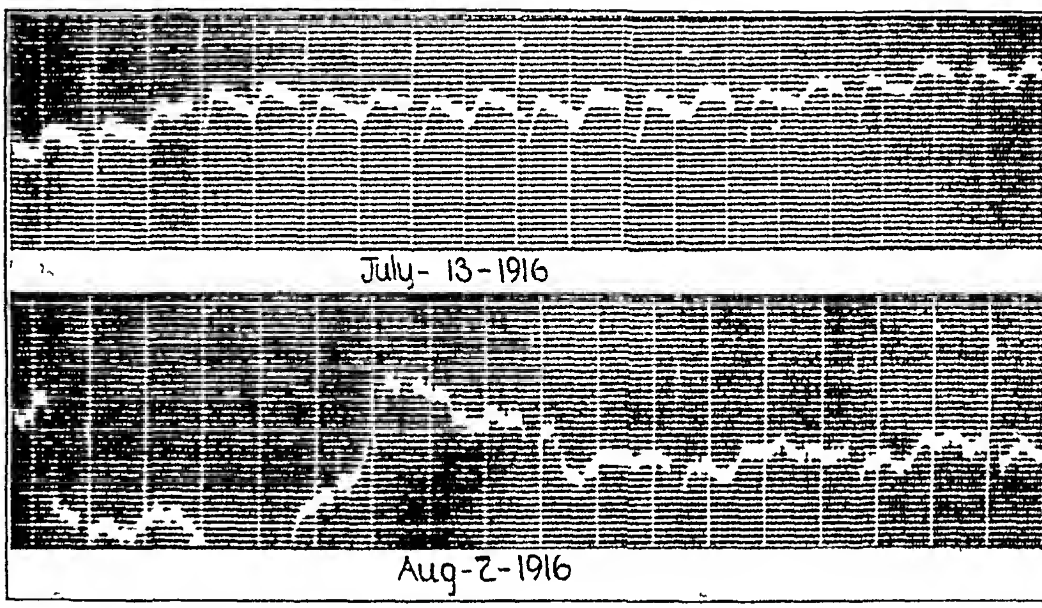

Fig 6 (92324) —1 Auricular flutter, auricular rate 292, ventricular rate 146 2 Fibrillation induced by digitalis, rate about 120

CASE 119641—A man, aged 39, came for examination Nov 24, 1914 He had suffered with hay-fever for years, and with asthma during the past year He came to the clinic during a paroxysm of tachycardia which had existed for two days The pulse was 212 constantly, with marked evidence of cardiac embarrassment These attacks had occurred twice within the year and had lasted six and eight days, beginning and terminating abruptly He was unable to retain any medicine, and in spite of the treatment died on the fifth day of his attack, three days after his arrival Before death the heart was greatly dilated and the pulse varied instantly from slow to rapid rhythm No tracings were possible after the first day No valvular lesion was demonstrated clinically or pathologically

CASE 142236—A man, aged 55, was admitted to the clinic Sept 28, 1915 The patient had been subject to "grippe," and five years before coming for examination had noticed dyspnea and spells of syncope with sudden onset He would fall whenever and wherever the spells came on At this time he rested six weeks and improved One year later (July, 1913) he had another attack which

lasted six weeks and which necessitated two weeks in bed April, 1914, another attack lasted a month, after which his health was good until July 7, 1915, when a sudden attack came on while he was eating supper This had persisted since with violent attacks of syncope During the first examination in the clinic the patient suddenly went into collapse He became cyanotic, pulseless and unconscious, there was extreme pallor and cold sweat Death seemed imminent, when the idea of vagal pressure suddenly occurred to one of us Pressure on the right vagus suddenly reduced the pulse rate (see cardiograms of similar pressure in another attack) to about 55, with prompt recovery of consciousness Fibrillation was induced three times during two months by digitalis therapy, only to have the flutter recur after its discontinuance The patient's fortitude in attempting a fourth course of treatment was rewarded by a return to a sinus rhythm on Christmas eve, and eighteen months later he reported that he was

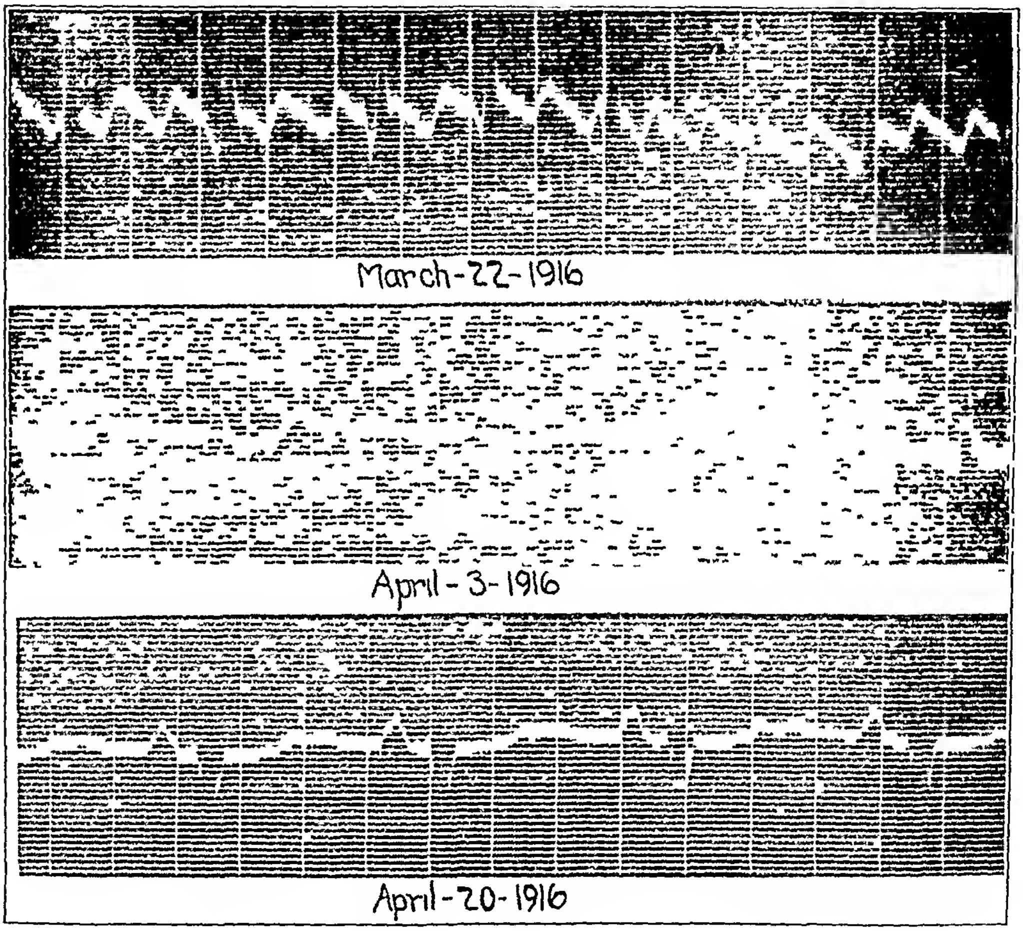

Fig 7 (145990) —1 Auricular flutter, 2-1 rhythm, auricular rate 340, ventricular rate 170 2 Fibrillation induced by digitalis 3 Sinus rhythm following thyroidectomy, rate 92

doing light farm work The heart was normal objectively between attacks except for occasional auricular extrasystoles

Case 142802—A woman, aged 32, was admitted to the clinic Oct 6, 1915 She had had repeated tonsillitis and a probable exophthalmic goiter She came for relief from biliary colic For several months she had been conscious of a "fluttering heart" and had had several spells of violent palpitation, usually following exertion Electrocardiograms showed a 320-160 rate ordinarily While under observation she came into the office with a ventricular rate of 320 (counted

by stethoscope) during a paroxysmal attack lasting nearly two hours She had walked several blocks to the office and was not sufficiently inconvenienced during the first hour to make complaint The rapidity was discovered on examination, when the ventricular rate was found to have fallen to 300 She walked up one flight of stairs for a cardiographic examination during the attack, which stopped suddenly while the examination was in progress and the usual 2-1 rhythm was reestablished This case is unique in that it is the fastest human

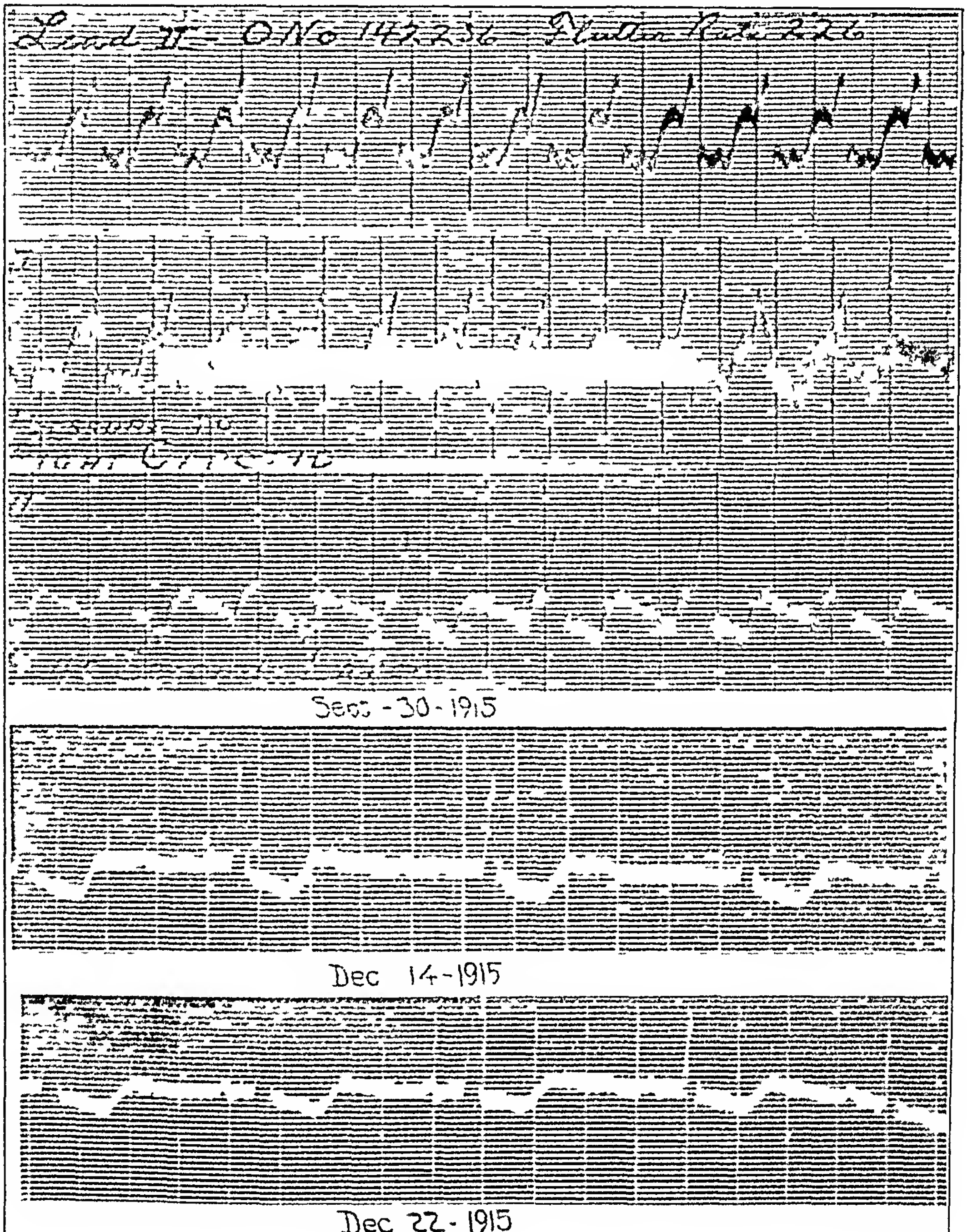

Fig 8 (142236) —1 Paroxysm of 1-1 flutter with 45 second intervals between the three strips, rate 224, pressure applied to right vagus indicated by arrow at beginning of second strip, 2-1 flutter established within a few seconds, as indicated in third strip 2 Fibrillation induced by digitalis, rate, 88 3 Sinus rhythm restored, rate 71, definite abnormal auricular rate

ventricular rate yet recorded The patient said she had suffered from such attacks repeatedly and that the present attack was milder than many of the others

Under digitalis medication fibrillation was induced but on its withdrawal flutter returned A second trial resulted similarly, a third attempt was made, and the patient while fibrillating was referred for cholecystectomy, which was successfully accomplished A sinus rhythm was established some days later (rate 120) and persisted for four months, until the flutter returned following heavy work cleaning house We obtained further tracings May 1, 1916, showing flutter, but the patient could not remain for treatment

This case had been diagnosed as exophthalmic goiter before the patient came to us and she was anxious to have a thyroidectomy We wished to defer operation on account of the heart condition and the questionable diagnosis of hyperthyroidism, and thyroidectomy was performed elsewhere (November, 1916) Pathologic examination of the tissue, which the surgeon kindly sent to us, showed the typical hyperplastic changes of exophthalmic goiter The patient reports a pulse practically normal and health restored since operation

Case 145990—A woman, aged 41, came for examination March 21, 1916 The patient had had tonsillitis repeatedly She had had the classical symptoms

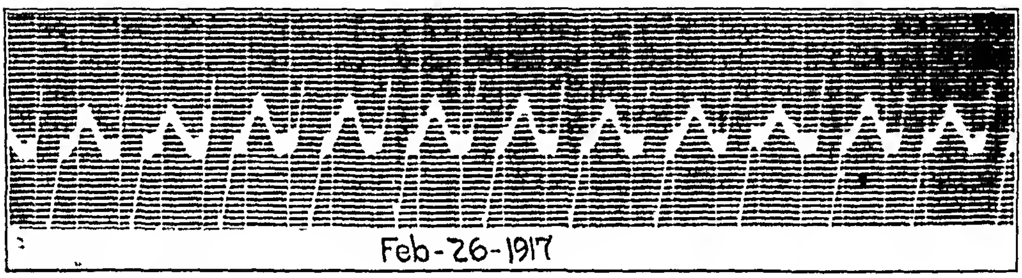

Fig 9 (130119)—Auricular flutter, auricular rate 300, ventricular rate 150

of exophthalmic goiter for four years Three months previously ligations had been done in the clinic No cardiac disorder was then suspected On returning for thyroidectomy she was prostrated by a prolonged paroxysm of tachycardia The cardiogram revealed flutter She was treated with digitalis, and thyroidectomy was done while the heart was fibrillating Sinus rhythm was restored soon after operation She gave the interesting history of a prolonged paroxysm of tachycardia the year before, during which syncope was so complete that she was thought to be dead Aug 10, 1917, the patient reported marked improvement in general health and no more spells of tachycardia

Case 146153—A man, aged 26, entered the clinic March 18, 1916 There was no history of previous infections, except typhoid in 1912 The tonsils appeared large and unhealthy Classical exophthalmic goiter with symptoms had existed for nine years, relatively mild symptoms until the last two years He had had three spells of vomiting and prostration, probably due to flutter The heart action had been irregular and rapid but no record was taken before the ligations were done here Nov 26, 1915 At the present examination the cardiogram showed typical auricular flutter Heavy digitalis medication, 29 c c in ten days, brought on fibrillation Thyroidectomy was performed April 10, 1917, and sinus rhythm was restored shortly after The patient reports Aug 7, 1917, "I have forgotten all about my heart"

Case 168507—A man, aged 43, was examined Aug 9, 1916 The patient gave a history of typhoid and he was subject to tonsillitis He came to the clinic because of recurrent attacks of appendicitis He appeared healthy A cardiographic examination was made on account of the irregular pulse After discovering the flutter we elicited a good history of sudden attacks of mild

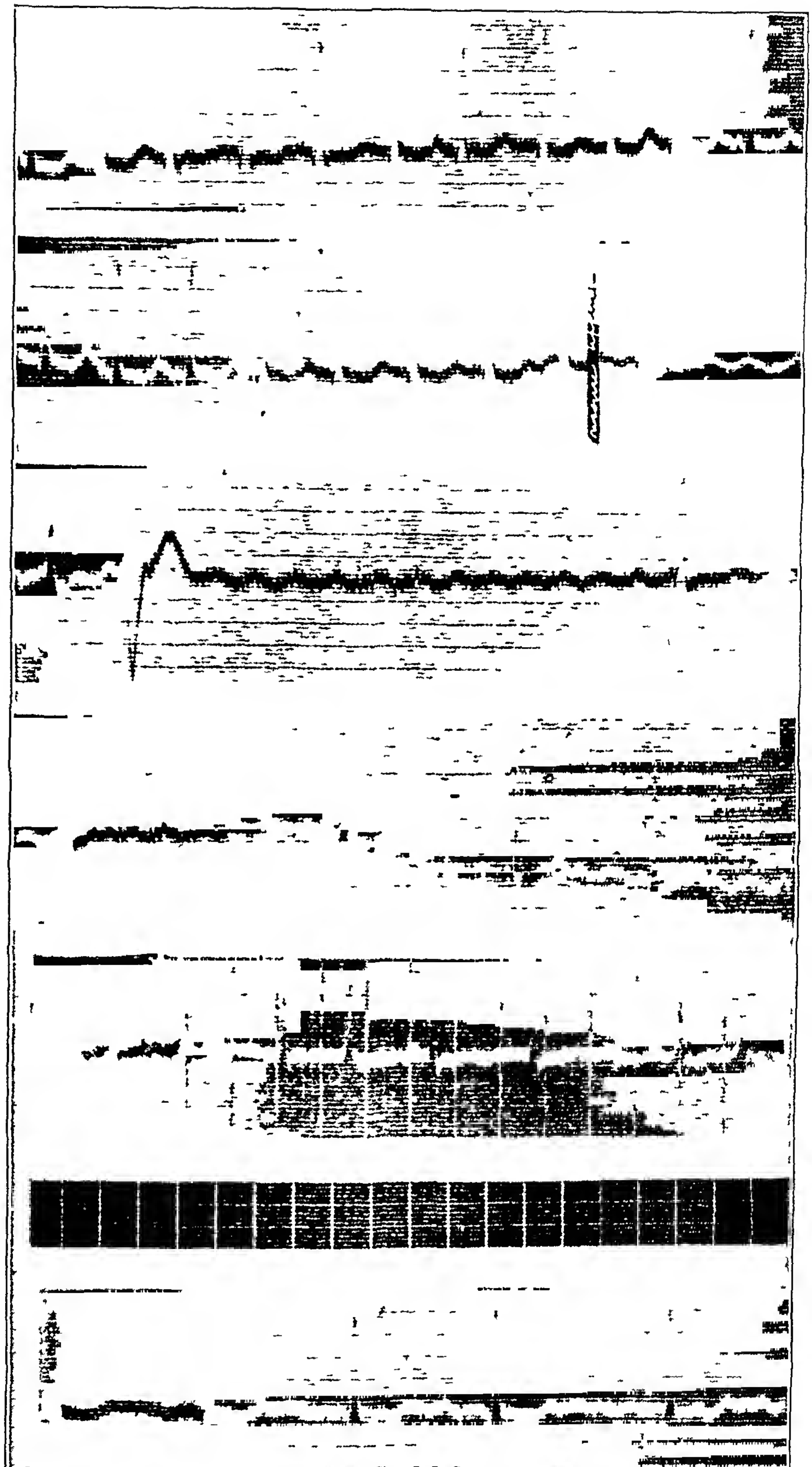

Fig 10 (195883) —1 Auricular flutter, 2-1 rhythm The top five strips are continuous tracings cut for reproduction Pressure applied at point indicated by interruption of light, cessation of ventricular action 4 5 seconds in third strip on release of pressure, series of ventricular extrasystoles as shown in fifth strip before resumption of normal rhythm 2 Lowest strip shows fibrillation under digitalis

syncope with rapid heart action, brought on by marked exertion during the previous five years Mild chronic dyspnea was also admitted The patient was treated thirty days, taking 100 c c of digitol before complete heart block and fibrillation were induced He left us then, but he has reported through his brother (Aug 12, 1917) that he feels well The appendix has not been removed

Case 158953—A man, aged 61, was examined May 5, 1916 Twelve months before admission, following grippe and mumps, the patient had had "nervous prostration," chief symptoms, nervousness, weakness and palpitation His physician told him the rapid pulse was due to "nervousness" November, 1915, there was again a sudden onset of rapid heart and weakness which has persisted to date He had "weak spells" and was dizzy With rapidity of the heart hoarseness was noticed He was treated with 69 c c digitalis twenty-three days before the onset of fibrillation Flutter recurred and the treatment was again instituted for a few days until the onset of fibrillation A few days later there was a second recurrence of flutter and again fibrillation was induced by digitalis Tonsillectomy was performed July 10 without incident The patient continued

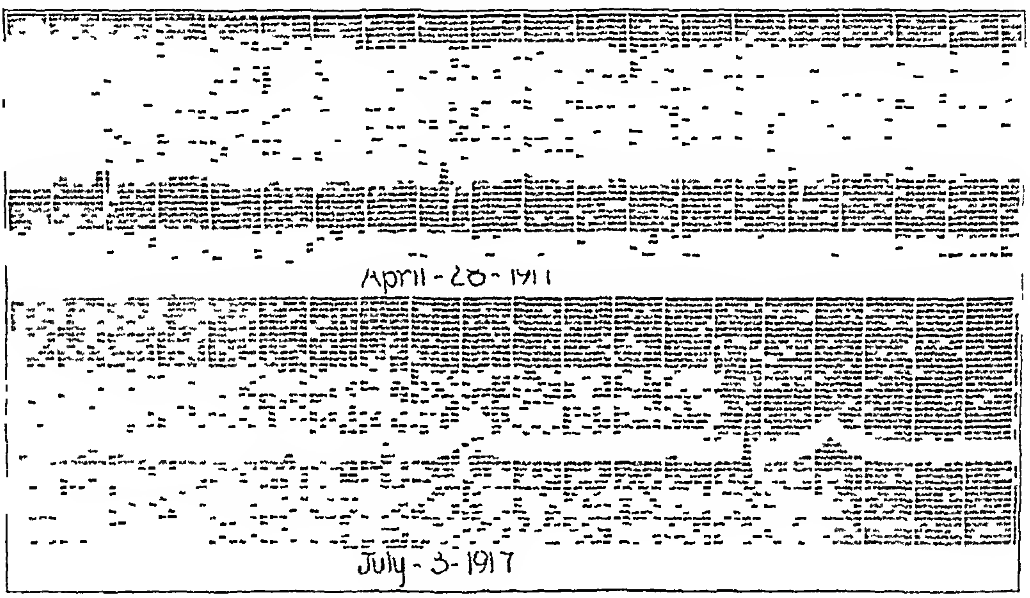

Fig 11 (192392) —1 Auricular flutter with complete heart block, 5-1 rhythm 2 Complete heart block

fibrillation without cardiac symptoms up to the last report From subjective sensations he was able to say accurately whether flutter or fibrillation was present No evidence of cardiac hypertrophy or valvular disease was obtainable at any time

Case 161186—A man, aged 75, a feeble, stiff, fat old man with marked sclerosis of the peripheral vessels and evident cardiac insufficiency, was examined May 31, 1916 He dated rheumatic symptoms back to rheumatic fever twelve years and four years previously Dropsy had been noted for a year but not much dyspnea or palpitation, probably because the rheumatism made exertion difficult Blood pressure 170-82 and pulse varying from 44 to 68, indicating impaired auriculoventricular conduction There was no valvular disease evident and the heart was not definitely large Treatment by rest and digitalis at home was recommended

Case 92324—A woman, aged 39, was admitted for examination July 12, 1916 Definite exophthalmic goiter, ligation performed in the clinic, October, 1913 At this time the pulse was regular, 95 to 118, and the heart greatly dilated

Thyroidectomy was performed, February, 1914, after marked improvement in the heart condition The patient returned the second time for observation All of the previous winter she suffered from frequent colds and grippe There was no history of syncope The first cardiogram taken showed flutter with 2-1 rhythm ventricular rate 196 Fibrillation was readily brought on with digitalis and continued during fifty-six days of observation

CASE 130119—A man, aged 52, was admitted for examination Feb 17, 1917 The patient had been operated on in the clinic, May 6, 1915, under local anesthesia for a small cyst of the tongue, but no general examination had been made at that time The patient was very obese, with evident marked cardiac

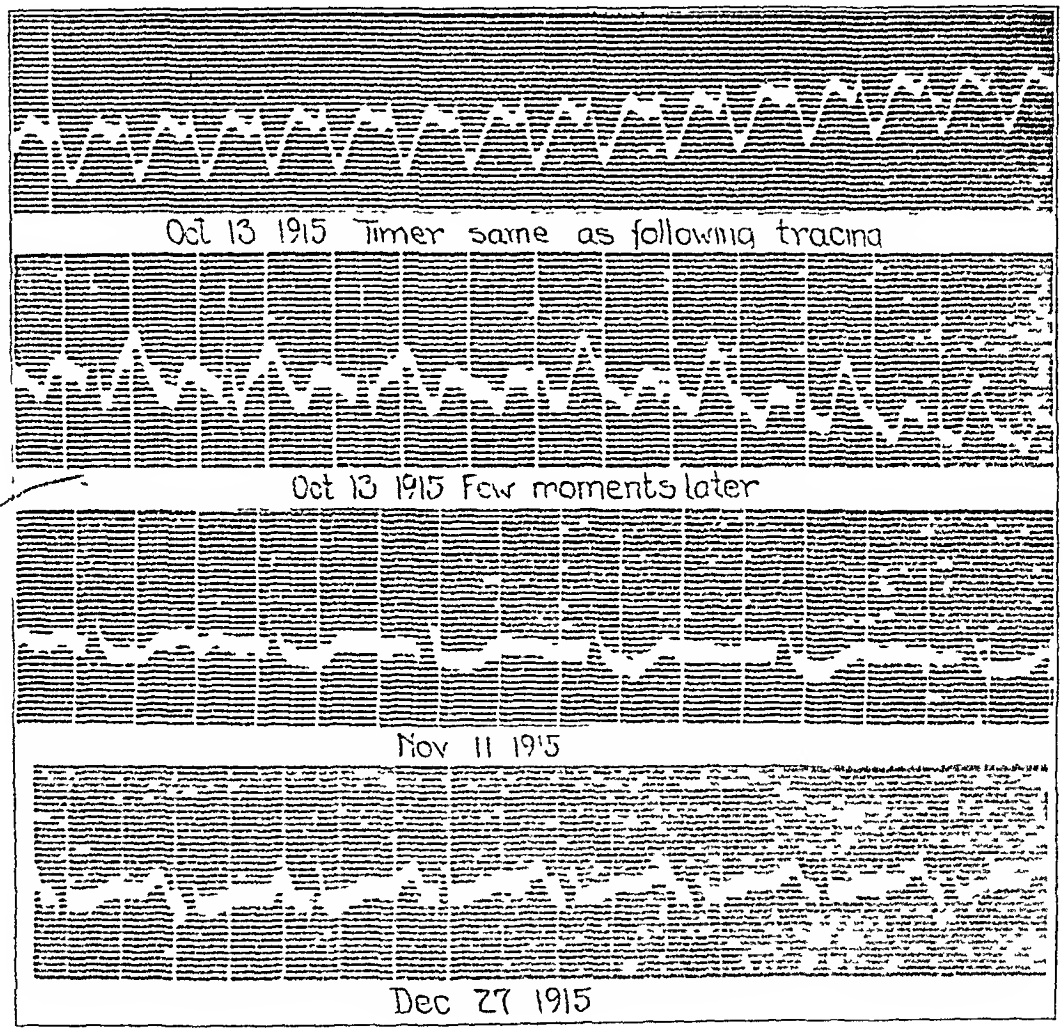

Fig 12 (142802) —1 Paroxysm of auricular flutter showing ventricular rate slightly above 300, timer same as next tracing 2 A few seconds later showing break in attack during the time necessary to change plates 3 Auricular fibrillation induced by digitalis 4 Sinus tachycardia, rate 130 following cholecystectomy and tonsillectomy This patient was operated on subsequently elsewhere for exophthalmic goiter four months following and at present reports normal heart action and pulse rate

insufficiency, and the roentgen ray showed diffuse dilatation of the aorta and the heart greatly enlarged Dyspnea had been noted twelve years, but marked cardiac insufficiency followed grippe last fall The cardiogram showed flutter The patient died suddenly on the fourth day in a coughing attack Necropsy revealed a fatty, dilated heart, and fatty sclerosis and dilatation of the aorta

Case 195883—A woman, aged 43, was admitted for examination July 1, 1917 The patient was subject to grippe She had had ten children The rapid heart action had been first noticed fourteen years previously during pregnancy There had been palpitation since on exertion, and last year there were repeated spells of very rapid heart action with palpitation Objectively the patient showed marked tachycardia (192) Pressure on the right vagus immediately slowed the pulse to about 60, releasing the pressure permitted the pulse go back to 192 She was treated with large doses of digitalis, and fibrillation was brought on in a few days Fibrillation continued since A slower pulse is definite evidence of double mitral lesion

Case 187575—A man, aged 45, was admitted for examination March 8, 1917 He had had typhoid twenty-seven years previously For two years he had been subject to attacks of dyspnea and pain in the precordium radiating to the epigastrium Worse attacks lasted one-half hour, causing complete incapacity The heart enlarged objectively but no valvular defect was noted The electrocardiogram showed typical flutter, auricles 224, ventricles 112 The second examination showed ventricles 224, and a 1-1 rhythm The patient was unable to remain for treatment

Case 192392—A man, aged 37, was admitted for examination Aug 25, 1917 He gave a history of a questionable sore on the penis at the age of 17, but we were unable to establish syphilis on a most searching investigation Apparently the man was strong and healthy There had been mild dyspnea on exertion for two years, but no definite attacks A month previously a sudden syncope followed very heavy lifting and the "right arm went dead for a little while" The heart was objectively negative except for a slow pulse (46) The electrocardiogram showed flutter, auricles 225 and ventricles 46 To rule out syphilis a therapeutic test was given, with no result after three weeks of treatment Digitalis was started and the next morning a second cardiogram showed a sinus rhythm with complete disassociation of ventricles (46) and auricles (72) The digitalis was stopped at once The condition had persisted since (three months) No further medication was used except potassium iodid for empirical reasons The patient suffered no subjective inconvenience and had no evidences of a Stokes-Adams syndrome

Case 145519—A thin, asthenic woman, aged 30, was admitted for examination Aug 2, 1917 Following pneumonia five years previously she had suffered with repeated weak spells associated with rapid heart action The pulse was always rapid, and at the examination averaged 133 Electrocardiogram showed auricular flutter, auricles 266, ventricles 133 This patient is to return for treatment

Case 204974—A man, aged 37, was admitted for examination Aug 17, 1917 The patient had been asthmatic all his life, but we were unable to elicit a history of previous infection He was a laborer and looked robust The heart had been very rapid for three years when at work, but there was no history of weak spells He was prepared for a cardiogram on account of irregular pulse Auricles 258 Ventricles 172 This patient is to return for treatment

Case 203875—A thin man, aged 52, was admitted for examination Aug 6, 1917 He was subject to colds Eight years previously he had an attack called "bilious" for three weeks The muscles were contracted and there was debility and weakness with sudden onset Morphin relieved the attack Since then repeated lighter "bilious spells" occurred and morphin was given to prevent the spasm These attacks occurred at intervals of weeks or months Podophyllum or morphin relieved the attacks There was mild chronic dyspnea and the electrocardiogram showed flutter The patient continued under treatment

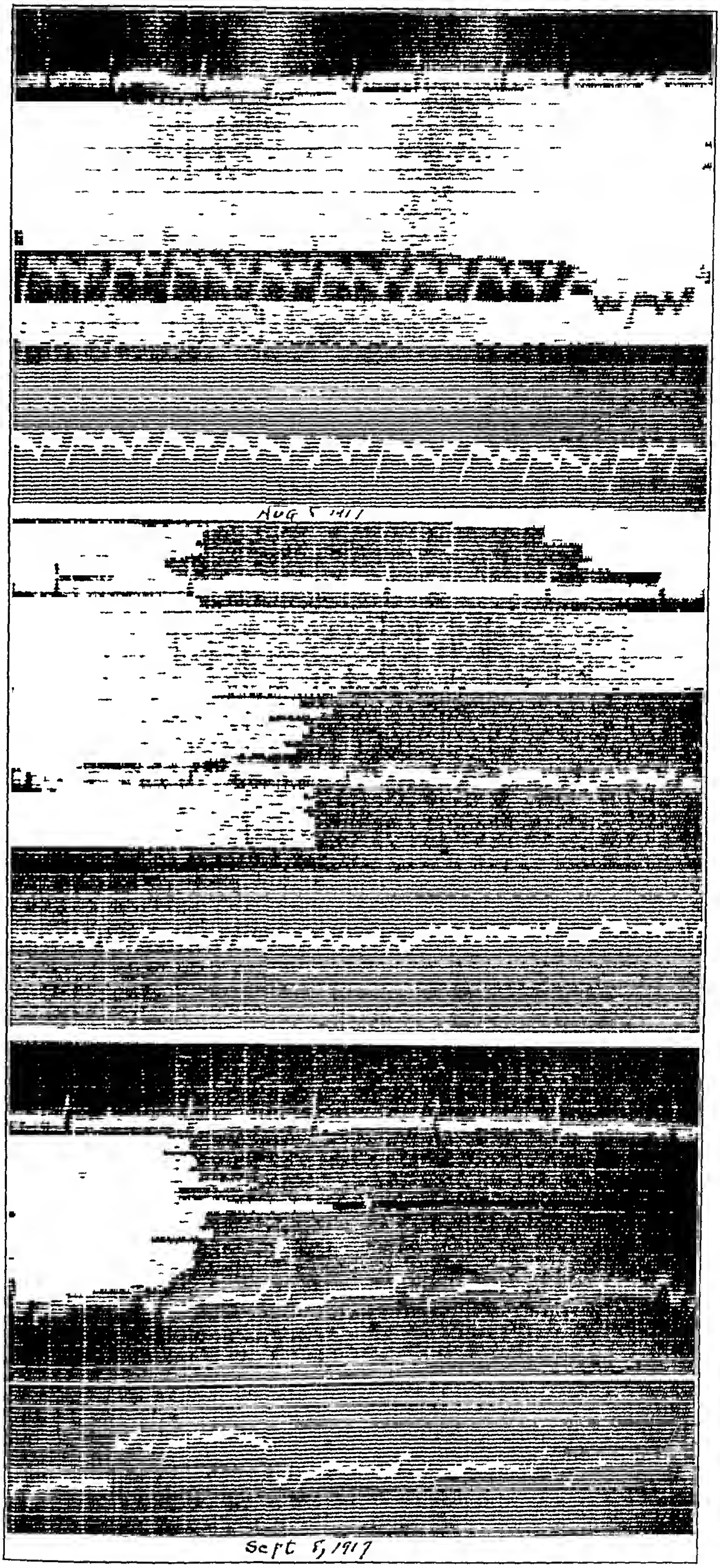

Fig 13 (203875) —1 Paroxysm of auricular flutter showing ventricular rate of 120 2 Twenty-six days later showing auricular fibrillation after heavy digitalis dosage 3 Sinus rhythm five days later

Treatment and Results—As Lewis has shown, digitalis has proved to be the sovereign remedy in cases of flutter We have used the drug in large doses, and have treated ten patients, not counting the two who were moribund and who died before any effect of medication was possible Two patients (Cases 161186 and 192392) were not treated for obvious reasons, and two (Cases 204974 and 187575) were unable to stay for treatment

The amounts of digitalis administered and a summary of the results are given in the accompanying table All the patients were in the hospital at complete rest during the digitalis medication Digitalis broke the flutter in all ten patients, and four finally resumed and held a normal rhythm The others were markedly improved subjectively by the onset of fibrillation

Table Showing Amounts of Digitalis Given and Summary of Results

Case	Onset of Fibrillation		Onset of Toxic Effects	
	Days	Amount, C c	Days	Amount, C c
142236	75	280	51	185
142802	42	220	26	180
145990	60	94	0	0
146153	8	29	0	0
158953	51	100	22	70
922324	4	12	0	0
168507	23	100	0	0
195833	16	51	0	0
203875	24	190	22	190

The most important point in the treatment is to use enough digitalis We have run up the dose rapidly to the physiologic tolerance of the patient Our maximum dosage was 10 5 c c daily for ten days before toxic effects were evident We have seen no bad results from such massive dosage except the temporary toxic symptoms, and we feel sure that most patients require massive dosage to obtain the desired result Further, we have found better results from pushing the drug to physiologic complete block if the patient tolerates it to this point, that is, far beyond the point of fibrillation in most instances In all our patients we have produced marked poisoning before discontinuing the drug In the four cured patients we repeatedly had the fibrillation break back to a flutter until digitalis poisoning was produced

The after-treatment is important We discontinue medication for cured patients, but have advised in fibrillating cases that digitalis be used, if necessary, to keep the pulse averaging below 80 when at rest The usual general advice to cardiopaths should always be emphasized

Operability.—One operation is reported in the literature—a death on the table under chloroform anesthesia attributed to flutter. We believe that if surgical treatment is indicated, particularly the removal of a probable source of infection or toxemia, the risk should be accepted. All operations have been performed after inducing fibrillation by digitalis and while the patient was under medication. We have been careful not to have atropin administered before operation, since this would temporarily abolish the vagus stimulation of the digitalis.

Three of our patients had exophthalmic goiter, and in two of these sinus rhythm and apparently normal health were regained after thyroidectomy. The third was a bad cardiopath, but sinus rhythm was restored, though the patient still has some symptoms of cardiac insufficiency.

Removal of the tonsils seemed advisable in cases in which there was evident focal infection, and this was done in two instances. One patient improved greatly, the other is subjectively cured. Cholecystectomy was done in one case.

SUMMARY

Auricular flutter occurs as a mechanical disorder in certain diseased hearts, and in our experience has been most frequently associated with exophthalmic goiter.

The paroxysmal attacks noted in fourteen of our sixteen cases are dangerous to health and even to life. Two patients died in such attacks and two others appeared so nearly dead as to deceive competent observers. The patient with flutter is always in danger of such attacks. He should always have the disorder arrested as soon as possible after its discovery.

In our experience efficient treatment may be relied on to cause the onset of fibrillation and greatly to relieve the patient. None of our patients is known to have had a recurrence of flutter after his dismissal.

Three patients were operated on under ether anesthesia for exophthalmic goiter after fibrillation was established, and one of these and one other have had tonsillectomies (local anesthesia) performed without incident. Cholecystectomy has been performed in one case.

All of the ten treated patients are alive and much improved or cured with treatment. Five report that they cannot detect any cardiac symptoms.

HEART-BLOCK

I TWO CASES OF COMPLETE HEART-BLOCK SHOWING UNUSUAL FEATURES *

FRANK N WILSON, M D, AND G CANBY ROBINSON, M D
ST LOUIS

The following two cases of complete heart-block are considered worthy of report because of several unusual features shown by electrocardiograms

REPORT OF CASES

CASE 1—Mrs E P, an American housewife, aged 39, had been under observation in the Washington University Dispensary for two years She first came to the dispensary because of various gynecologic complaints associated with retroversion of the uterus At that time it was found that she had an unusually slow pulse rate, and electrocardiograms revealed the presence of complete heart-block This condition had been constantly present since, but in spite of this fact she had had no cardiac symptoms aside from slight dyspnea on exertion She had never had a syncopal attack Physical examination of her heart had constantly shown moderate enlargement of the cardiac dulness, the presence of an apical systolic murmur transmitted to the axilla, and a faint aortic systolic murmur poorly transmitted The patient's past history revealed no infections which might account for the cardiac condition aside from frequent attacks of tonsillitis during childhood The Wassermann reaction was negative When she was 19 years old, she was told by a physician that her pulse rate was only about one half the normal, so that it seems likely that the heart-block had been present for at least twenty years

CASE 2—Mr M R, a German cigarmaker, had been under observation in the Barnes Hospital and the Washington University Dispensary since March 31, 1917 He presented himself on that date complaining of syncopal attacks, vertigo, and dyspnea on exertion During the previous seven weeks he had had five syncopal attacks of short duration, all of which came on without warning and without any apparent exciting factor None of these attacks followed exertion Between attacks he was troubled by vertigo on turning quickly and by dyspnea on exertion Physical examination revealed moderate enlargement of the cardiac dulness and a faint systolic murmur was heard over the whole precordium The heart was beating regularly at the rate of 36 per minute There was a moderate arteriosclerosis Electrocardiograms showed the presence of complete heart-block The past history and the laboratory findings, including the Wassermann reaction, were negative

DISTURBANCES OF AURICULAR ACTIVITY

The electrocardiograms revealed a tendency in both patients for those interauricular periods during which a ventricular systole occurred to be shorter than those which followed them (Figs 1 and 2) This

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* From the Department of Internal Medicine, Washington University Medical School

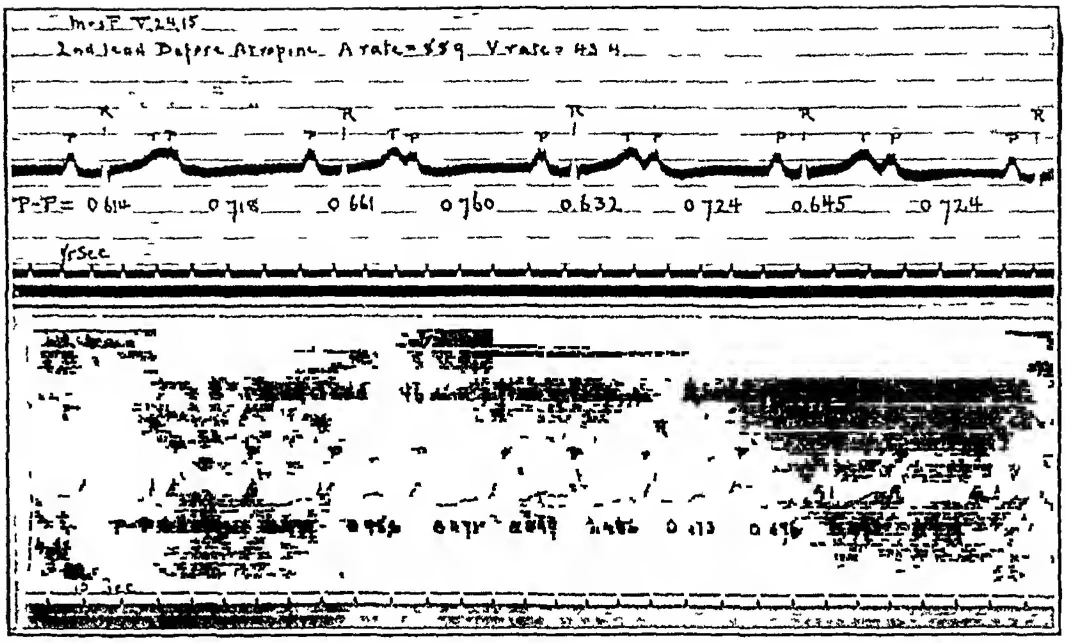

Fig 1 (Case 1 Lead II) —Complete heart-block Atropin produced an acceleration of both the auricular and ventricular rates and caused the auricular arrhythmia to disappear

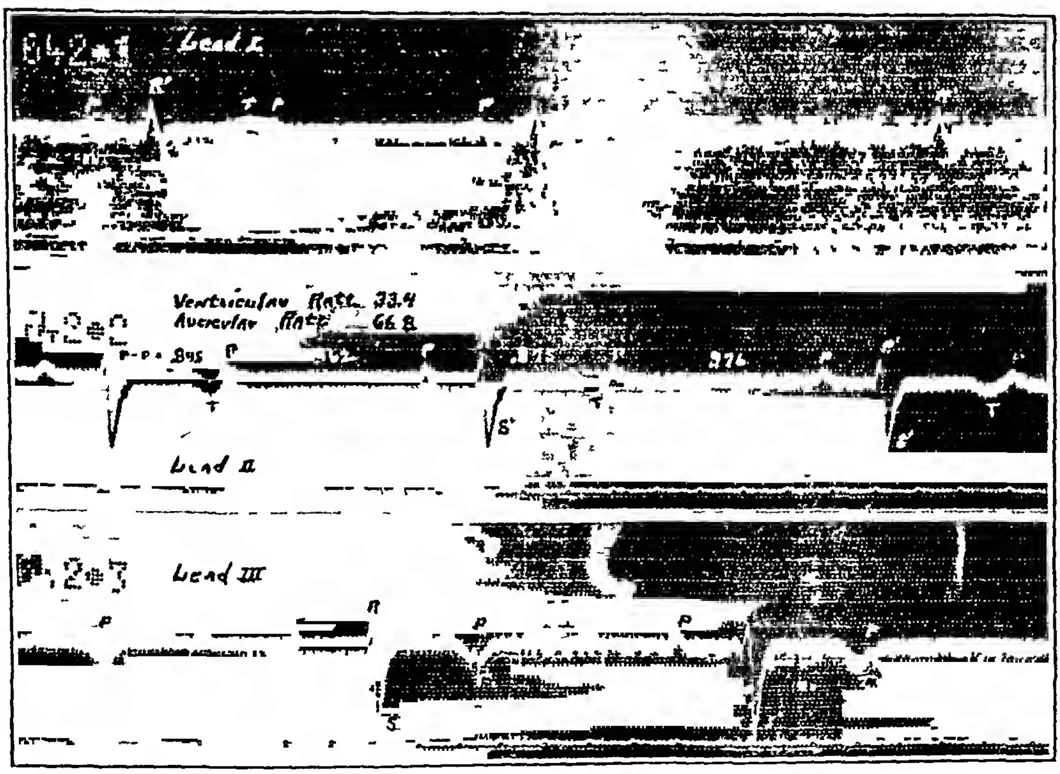

Fig 2 (Case 2) —The usual cardiac mechanism Complete heart-block, auricular rate 66.8, ventricular rate 33.4 Those auricular periods which contain a ventricular contraction are shorter than the others

tendency was observed only when the auricular rate was comparatively slow, it was not definitely present when the auricular rate was rapid, as after exercise or after the administration of atropin (Fig 1) This type of auricular arrhythmia has been previously described by Hecht,[1] who observed it in a case of complete heart-block in a child This author offers no explanation for its occurrence Erlanger and Blackman[2] have described a similar auricular arrhythmia in experimental heart-block They found that each ventricular systole produced a marked slowing of the auricular rate In marked instances this slowing was so great that only one auricular beat occurred during each interventricular period, when several auricular beats occurred between two consecutive ventricular beats, the first interauricular interval was long and the following auricular periods became gradually shorter Erlanger and Blackman ascribed this type of auricular arrhythmia to

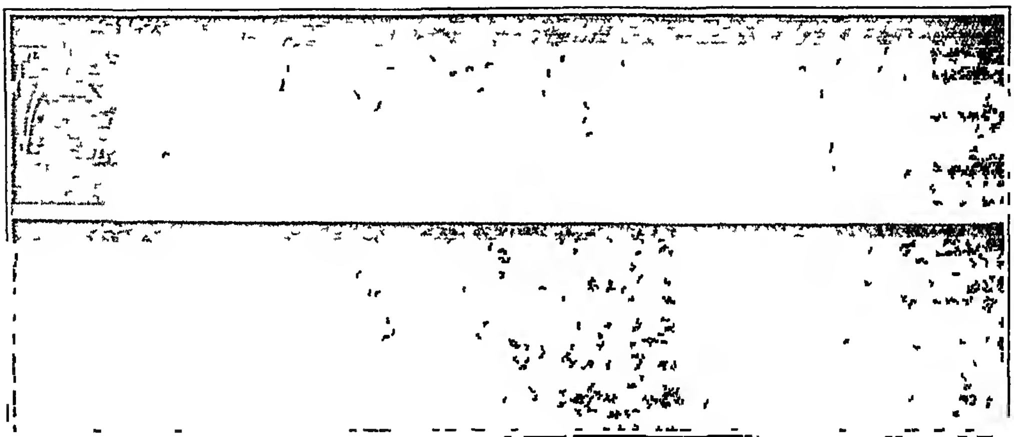

Fig 3 (Case 2)—Ectopic auricular beats represented by inverted auricular complexes occur when an auricular contraction is due shortly after the beginning of ventricular systole

rhythmical "variations in vagal tone, vagus inhibition increasing with each arterial pulse and diminishing again between pulses" It is quite possible that the auricular arrhythmia observed in our patients was the result of a similar mechanism The absence of the arrhythmia when the heart rate was fast after exercise and after atropin (Fig 1) lends support to the view that it was dependent on vagus activity

The occurrence of another type of auricular disturbance in one of our patients leads us to believe, however, that another explanation of this arrhythmia is possible In Case 2 a peculiar type of ectopic beats frequently occurred These beats are represented in the electrocardiograms (Fig 3) by inverted auricular complexes (in Leads II and III)

1 Hecht, A F Ergebn d inn Med u Kinderh, 1913, **11,** 324
2 Erlanger and Blackman Heart, 1909-1910, **1,** 177

occurring from 0 20 to 0 34 second after the beginning of the QRS group of the ventricular complex These abnormal auricular complexes appear only when a normal P wave is almost due at this point They bear, therefore, a fairly constant relationship to both auricular and ventricular systoles They differ from ordinary extrasystoles in this respect, and also because they occur so very late in auricular diastole On the other hand, it is impossible to believe that they represent retrograde auricular contractions, which they somewhat resemble, because of the presence of complete heart-block Similar ectopic beats have been observed in a case of complete and incomplete heart-block by Cohn and Fraser,[3] and these authors mention their occurrence in a case of complete heart-block studied by Parkinson They attribute their occurrence to the mechanical effect of ventricular systole on some ectopic auricular center In our case, as well as in that described by Cohn and Fraser, the form of the abnormal complexes indicates that this center was situated in each case, in the lower auricular or upper junctional tissues, and it seems likely that it was located in the specialized tissues to be found in that region We must assume that ventricular systole hastened the discharge of the stimulus in this center, and it seems possible that a similar effect of ventricular systole on the ordinary auricular pacemaker may account for the auricular arrhythmia discussed in the foregoing A careful study of the electrocardiograms has not enabled us to decide with confidence between this explanation and the one advanced by Erlanger and Blackman, which was mentioned previously

The effect of ventricular systole on the auricular period may explain another interesting phenomenon observed in both patients It sometimes happened — frequently and for long periods in Case 2, less frequently and for shorter periods in Case 1 — that the auricular rate was exactly twice the ventricular Whenever this occurred, the relationship of the auricular contractions was always nearly the same, and was of such a nature that every alternate auricular complex fell on the T wave It can be easily understood that this relationship might be brought about by a tendency for ventricular systole to bring about an auricular contraction at this point This relationship between the positions of auricular and ventricular contractions, when the auricular rate is an exact multiple of the ventricular, may lead to the diagnosis of partial block when complete block is really present This fact has also been noted by Erlanger[4] It is only when the ratio of auricular rate to ventricular rate is disturbed by exertion, or some other factor, that the true cardiac mechanism becomes evident

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3 Cohn and Fraser Heart, 1914, **5**, 141

4 Erlanger Personal communication

In Case 1 an entirely different type of auricular disturbance was observed This disturbance consisted in a very marked change in the form of the P wave in the third lead The usual form of the P wave in this lead is shown in the first six cycles of Figure 4 In the seventh cycle of this figure the P wave becomes very much larger and broader This change in the form of the P wave was observed in this patient on two occasions Each time it was accompanied by a definite increase in the auricular rate We have observed similar changes in the form of the P wave in other patients and in normal individuals, they are usually accompanied by a change in rate and are usually most marked in Lead III We believe that they are due to changes in the location of the pacemaker within the sino-auricular node, similar to the change in location of the pacemaker within this node which has been shown to occur in the experimental animal under the influence of vagus stimulation [5]

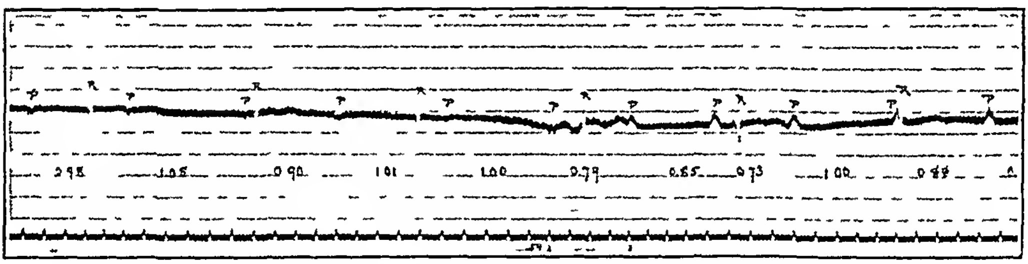

Fig 4 (Case 1) —A spontaneous change in the form of the P wave accompanied by an increase in auricular rate

THE VAGI AND THE IDIOVENTRICULAR RATE

There has been considerable discussion in the past as to whether the vagi exert any chronotropic influence on the independently beating mammalian ventricles The question has been repeatedly investigated both experimentally and clinically As a result of the clinical investigations, it has been well established that in the majority of the cases of complete heart-block, pressure on the vagus nerves in the neck and the administration of atropin do not produce any change in the ventricular rate In a few cases, however, the administration of atropin has produced a definite ventricular acceleration Such cases have been reported by Hecht[1] and by Hart [6]

Vagus pressure and atropin experiments were carried out on each of our patients Pressure on the vagi in the neck failed to affect the ventricular rate in either The subcutaneous administration of one-

5 Lewis, Meakins and White Phil Tr Roy Soc, London, Series B, 1914, **205,** 375

6 Hart, T S Am Jour Med Sc, 1915, **149,** 62

fiftieth grain of atropin in Case 1 increased the auricular rate from 89 9 to 124 4 per minute and the ventricular rate from 43 4 to 60 0 per minute (Fig 1) In Case 2, atropin increased the auricular rate from 74 to 96 beats per minute, but failed to affect the ventricular rate

Two general hypotheses have been advanced to explain such findings According to the first of these, the influence of the vagi on the idioventricular rate is dependent on the site of the lesion producing the block, and consequently on the level within the junctional tissues at which the ventricular pacemaker is located as described by Zander[7] If this is true, in the majority of the cases of complete heart-block the lesion, and consequently the ventricular pacemaker, is situated relatively low down in a region not subject to vagus control, but in an occasional case the lesion and ventricular pacemaker are located at a higher level in a region which is normally under the control of the vagi Organic structural lesions may occur in any portion of the His bundle, but the recent experimental work of Lewis, Meakins and White[8] indicates that functional block usually has its site in the region of the A-V node It seems likely, therefore, that, if the influence of the vagi on the ventricular rate is dependent on the site of the lesion, the chronotropic influence of the vagi on the ventricles would be more marked in functional than in organic heart-block There is not sufficient data at hand, however, to determine this point The greatest objection to this whole hypothesis is the fact that the idioventricular electric complexes, which occur when complete block is brought about in animals by vagus stimulation, are usually markedly abnormal and distinctly different from those seen when complete block is produced by other means (Kahn[9]), and also different from the ventricular complexes which usually occur in clinical complete heart-block This unquestionably indicates that the vagi do exert an influence on that region within the junctional tissues which lie above the bifurcation of the His bundle, a region which, judging from the usual form of the ventricular complexes in complete heart-block, contains the idioventricular pacemaker

According to the second hypothesis which has been advanced to explain the established facts with regard to the vagi and the idioventricular rate, the region which contains the idioventricular pacemaker is normally subject to vagal influence, but this influence is destroyed by the same lesion which produces the block (Lewis[10])

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7 Zander, E Nord med Ark, 1915, **2,** No 6, Part 2 Reviewed in Zentralbl f Herz u Gefasskrank, 1915, **19,** 1914

8 Lewis, Meakins and White Heart, 1914, **5,** 289

9 Kahn, R H Ergebn d Physiol, 1914, **14,** 1

10 Lewis, T Lectures on the Heart, New York, Paul B Hoeber Company, 1915

This might easily occur if, as is probable, the majority of the vagus fibers reach the ventricles by way of the A-V bundle Advocates of this theory have, so far as we know, not attempted to explain the occurrence of cases, such as one of those which we are reporting, in which, in spite of the presence of complete block, the ventricular rate is subject to vagal influence The occurrence of such cases is, however, not an insuperable objection to the theory, for it has been shown by Garrey[11] that the passage of the excitation wave through a layer of muscle may be interrupted by compression without preventing the passage of nerve impulses through the same area It is possible also that a lesion may be so located as to interrupt the muscular without interrupting the nervous connection between auricles and ventricles

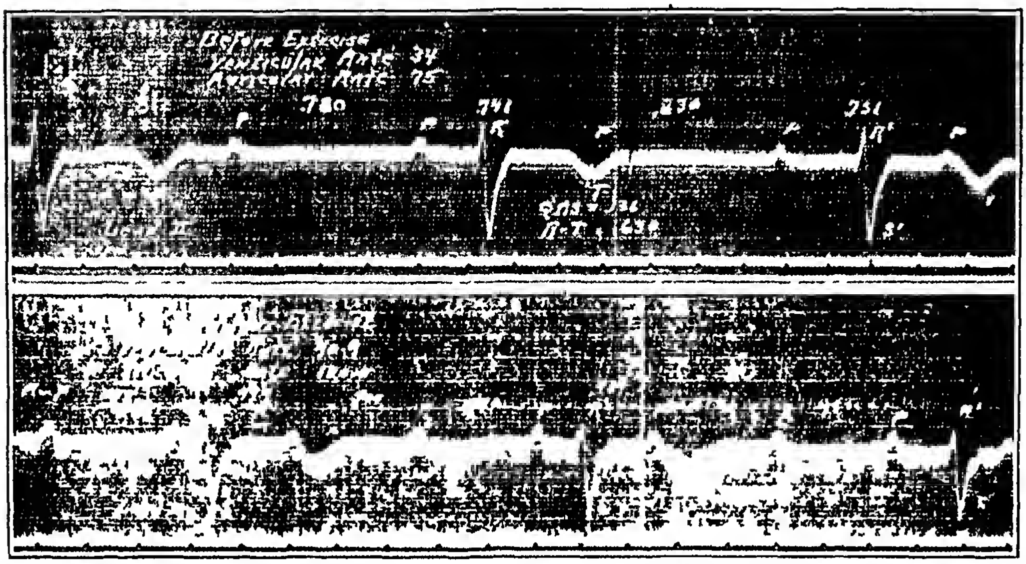

Fig 5 (Case 2)—The effect of exercise on the cardiac mechanism The auricular rate is markedly intensified, and the ventricular rate only slightly increased

We also investigated the effect of exercise on the cardiac rate in one of our cases (Case 2, Fig 5) The exercise consisted in doing 3,300 foot-pounds of work in thirty seconds by climbing stairs Electrocardiograms were taken immediately before and after the exercise The auricular rate was increased from 75 to 120 per minute and the ventricular rate from 34 to 40 per minute According to Gasser and Meek[12] exercise may increase the heart rate in four distinct ways (1) by an inhibition of vagus activity, (2) by an increase of accelerator activity, (3) by an increase in the secretion of epinephrin, and (4) by an increase in the temperature of the blood They found that the first of these mechanisms was by far the most important Since

11 Garrey Am Jour Physiol, 1911, **28**, 249
12 Gasser and Meek Am Jour Physiol, 1914, **34**, 48

the ventricular pacemaker in our patient was apparently not under the control of the vagi, the increase in the ventricular rate observed after exercise must have been due to the last three factors mentioned Erlanger and Hirschfelder[13] have shown that the idioventricular rate in complete heart-block is subject to accelerator influence, and the other two factors concerned would probably act without reference to the location of stimulus production The slight increase in the ventricular rate as compared with the marked auricular acceleration indicates the great disadvantage from which patients with complete heart-block suffer during exercise as a result of the loss of vagus control of the ventricular rate

DISTURBANCES OF VENTRICULAR ACTIVITY

In Case 2, two distinct disturbances of ventricular activity were observed On one occasion there was a spontaneous change in the form of the ventricular complex (Fig 6) This was not accompanied by any definite change in rate, and two possibilities offer themselves for its explanation there was either a change in the location of the ventricular pacemaker, or a change in intraventricular conduction at this time This phenomenon may have been caused by a massive dose of the tincture of digitalis which had been administered twenty-three hours before it was observed

The second disturbance of ventricular activity shown by this patient was a marked tendency to multiple ventricular extrasystoles after exertion Multiple extrasystoles could be produced almost at will by having the patient rapidly perform about 3,000 foot-pounds of work by climbing stairs They were first observed about twenty-three hours after the administration of a massive dose of digitalis, but could be produced as long as the patient remained under observation The extrasystoles were not always of the same type and they occurred at a very rapid rate (Fig 7) Single extrasystoles were observed during the same period and the number occurring in succession varied from two to eight These extrasystoles did not occur immediately after the cessation of effort, but about two to three minutes later, and there was usually considerable variation in the form of the ventricular complex at the time of their appearance At first it was thought that there was some relationship between the tendency to multiple extrasystoles after exertion and the administration of the digitalis, but the fact that this tendency continued unabated for a period of sixteen days after the digitalis had been given makes this relationship doubtful

It is also interesting to speculate on the relationship of this tendency to multiple extrasystoles and the syncopal attacks which the patient

13 Erlanger and Hirschfelder Am Jour Physiol, 1905-1906, **15,** 153

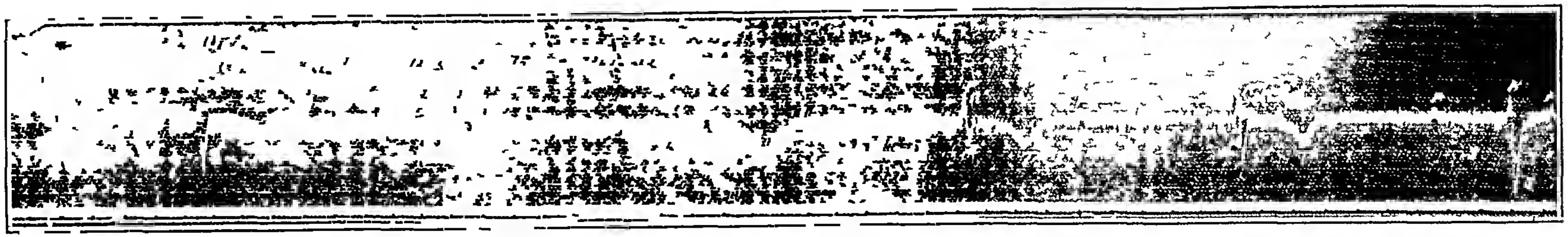

Fig 6 (Case 2) —A spontaneous change in the form of the ventricular complex

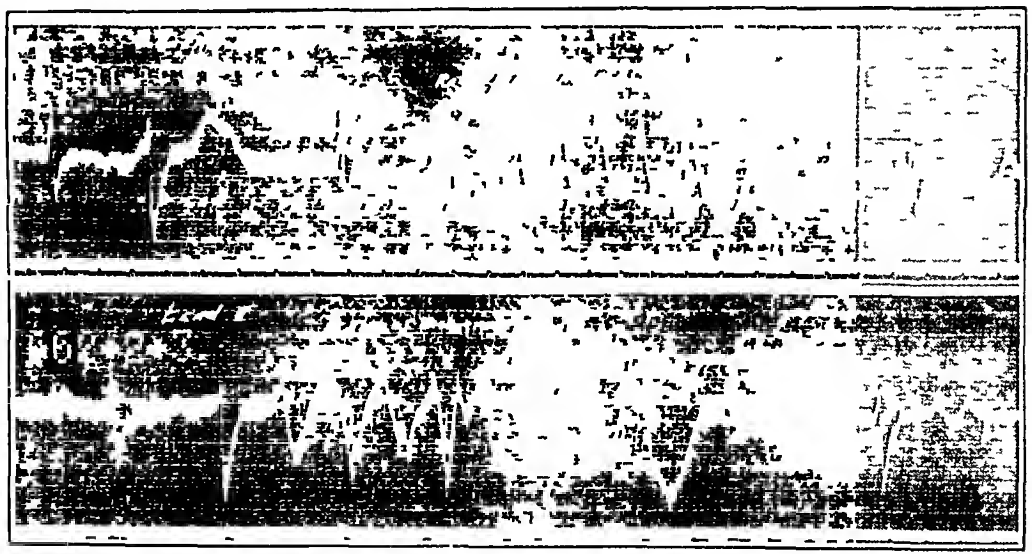

Fig 7 (Case 2) —Multiple extrasystoles after exercise

had Ventricular tachycardia might conceivably produce such attacks, if sufficiently long continued, and, moreover, it is possible that the ordinary pacemaker might fail to take up the rhythm promptly after its interruption by such a series of ectopic beats as in a case observed by Lewis[10] As the patient had no syncopal attacks while under observation, no direct evidence could be obtained on this point Against the existence of any causal relationship between the multiple extrasystoles and the syncopal attacks is the fact that the latter never occurred after effort, while the former occurred at no other time during the period that the patient was under observation The constant appearance of multiple extrasystoles after exercise in this case suggests that exertion may have influenced the nutrition of the heart unfavorably and thus led to their production This idea is borne out by observations on a patient with angina pectoris who developed an idioventricular tachycardia on exertion

SUMMARY

Two cases of complete heart-block showing unusual features are reported The following phenomena were observed

1 Auricular arrhythmia dependent on ventricular activity

2 Ectopic auricular beats dependent on stimuli received from the contracting ventricles

3 Increase in the idioventricular rate after the administration of atropin

4 Multiple ventricular extrasystoles after exertion.

5 Spontaneous changes in the form of the auricular and of the ventricular complexes

The explanation of these phenomena is discussed

THE RATE OF ABSORPTION AND EXCRETION OF THE IODIDS OF STRONTIUM, SODIUM AND POTASSIUM *

E J KRAHULIK, M D, AND J D PILCHER, M D
OMAHA CLEVELAND

Strontium salts have been used to a limited extent in therapeutics for the effect of the bromid, iodid or salicylate radical, but their use has been more or less discouraged because it was thought that the strontium salts were more slowly absorbed than the corresponding salts of sodium and potassium [1]

Since all iodids would exist in the blood and tissues essentially as sodium iodid, the excretion would be the same irrespective of the cathion, provided, of course, that the other conditions were the same Consequently, any difference in the excretion of the iodid in the urine would indicate that the change was primarily in the absorption of the original iodid Iodid was chosen in this investigation because its normal excretion has often been determined and because its quantitative estimation is simple and accurate The excretion of strontium iodid was compared with that of sodium and potassium

Method—The investigation was made chiefly on one subject, but for comparison a lesser number of experiments were made with the strontium and sodium salts, only, on two other individuals Each subject led a fairly uniform life during the investigation The iodid was taken immediately after a uniform breakfast and the total urine collected at the following periods ½, 1, 2, 6, 12, 24, 48 and 72 hours At least three experiments were made with each drug, with a minimum interval of four days between experiments to insure the complete excretion of the previous dose The iodid was estimated by the usual methods [2] The averages of the iodid excreted at the different periods

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* Submitted for publication July 31, 1917

* From the Pharmacological Laboratory, School of Medicine, University of Nebraska

* The investigation was undertaken at the request of the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry of the American Medical Association

1 Cushny Pharmacology and Therapeutics, 1915, p 567

2 Convenient quantities of urine (10 to 50 c c) were evaporated in nickel crucibles with 1 gm potassium hydroxid and 0 5 gm potassium nitrate per 10 c c of urine, fused and dissolved in water, made acid with 10 per cent sulphuric acid and 10 drops of 10 per cent sodium nitrite added, and the liberated iodin extracted with carbon disulphid and titrated with hundredth normal thiosulphate

and the total excretion are given in Table 1, the percentages in Table 2 The results are graphically illustrated in Figures 1 and 2 (As the results were similar in the different subjects the excretion of one, only, is given in the figures)

The iodid content of the salts as determined by analysis was as follows

NaI — 0 784 gm per gm
SrI — 0 525 gm per gm
KI — 0 722 gm per gm

TABLE 1—QUANTITY OF IODIN IN THE URINE AT THE SEPARATE PERIODS, AND TOTAL EXCRETION IN GRAMS OF IODIN

Hour	NaI 1 Gm	Total	SrI 1 Gm (× Factor)	Total	SrI 1 5 Gm	Total	KI 1 09 Gm	Total	NaI* 1 Gm	Total	SrI* 1 Gm (× Factor)	Total
½	0 0063		0 0057		0 0053		0 0082					
1									0 0298	0 0298	0 0291	0 0291
2	0 0871	0 0934	0 0816	0 0873	0 1103	0 1156	0 1022	0 1104	0 0581	0 0879	0 0897	0 1188
6	0 2023	0 2957	0 2116	0 2989	0 2181	0 3336	0 2197	0 3301	0 2182	0 3061	0 2175	0 3363
12	0 1562	0 4519	0 1748	0 4737	0 1791	0 5126	0 1705	0 5006	0 1700	0 4765	0 1400	0 4763
24	0 1524	0 6043	0 1268	0 6005	0 1731	0 6858	0 1545	0 6551	0 1288	0 6053	0 1753	0 6516
48	0 0771	0 6813	0 0942	0 6948	0 0861	0 7719	0 0796	0 7347	0 0542	0 6595	0 0540	0 7056
72	0 0108	0 6921	0 0130	0 7078	0 0162	0 7881	0 0239	0 7586				

* Subject P, all others from Subject K

TABLE 2—AVERAGE TOTAL IODIN EXCRETION IN PERCENTAGE OF THE INTAKE IN GRAMS OF IODIN

Hour	NaI 1 Gm	SrI 1 Gm	SrI 1 5 Gm	KI 1 Gm	NaI* 1 Gm	SrI* 1 Gm
½	0 8	0 72	0 68	1 0		
1					3 8	3 7
2	11 8	11 1	14 7	14 1	11 2	15 2
6	37 7	38 0	42 5	42 1	39 0	42 6
12	57 6	60 1	65 4	63 8	60 8	60 8
24	72 8	76 5	87 5	83 5	77 2	82 8
48	82 6	88 4	98 4	93 7	84 1	90 0
72	88 3	90 3	100+	96 7		

* Subject P, all others from Subject K

One gram of sodium iodid was the standard dose, 1 5 gm of strontium iodid and 1 09 gm of potassium iodid gave equal amounts of iodin In several experiments but 1 gm of strontium iodid was taken, so that in the tables and figures the results are multiplied by the correct factor as indicated

Rate of Excretion—There is practically no difference in the rate of excretion of the iodids of strontium, sodium and potassium as illustrated in Figure 1, which shows an increasing excretion rate reaching the maximum at about the sixth hour and then decreasing rapidly; during the third day but 10 to 20 mg were excreted in all

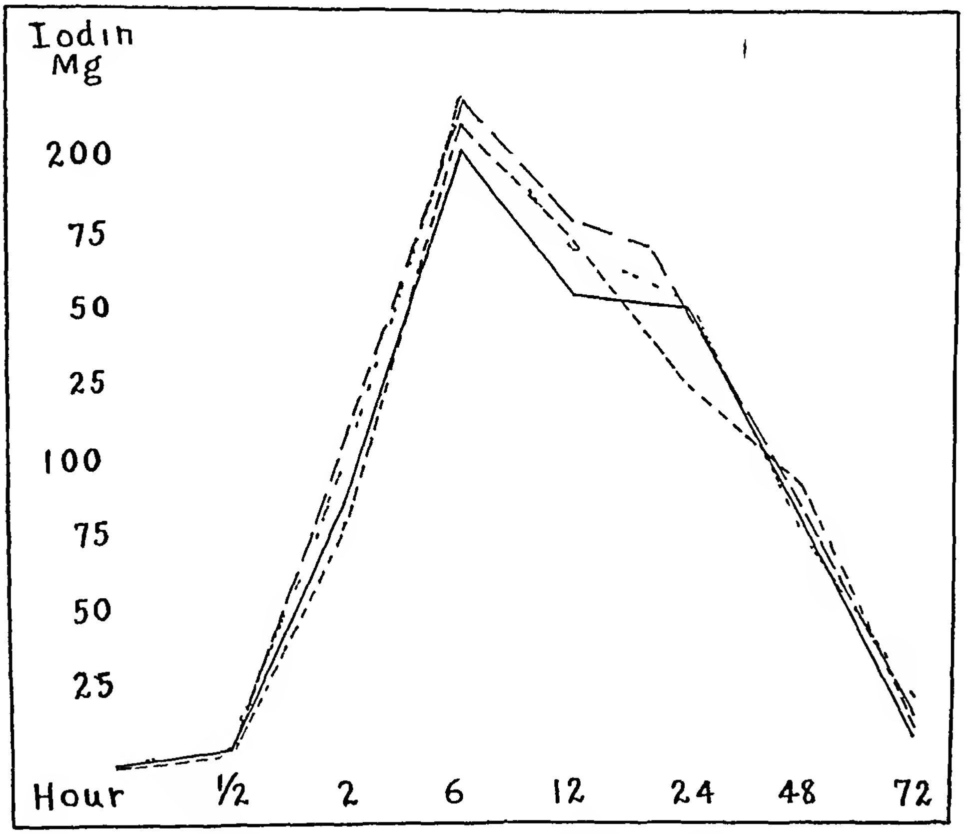

Fig 1—Rate of excretion of iodin in milligrams (Subject K), ——— sodium iodid, potassium iodid, — — — — strontium iodid, - - - - - - strontium iodid x factor

Total Excretion—A somewhat greater quantity of the strontium iodid than of the sodium iodid was excreted at the twenty-four, forty-eight and seventy-two hour periods, the potassium iodid (one subject) excretion lay between the strontium series As can be seen from the tables and figures, the difference is slight and probably of no significance

There seemed to be no definite ratio between the excretion of the iodid and the volume of urine There were instances in which a

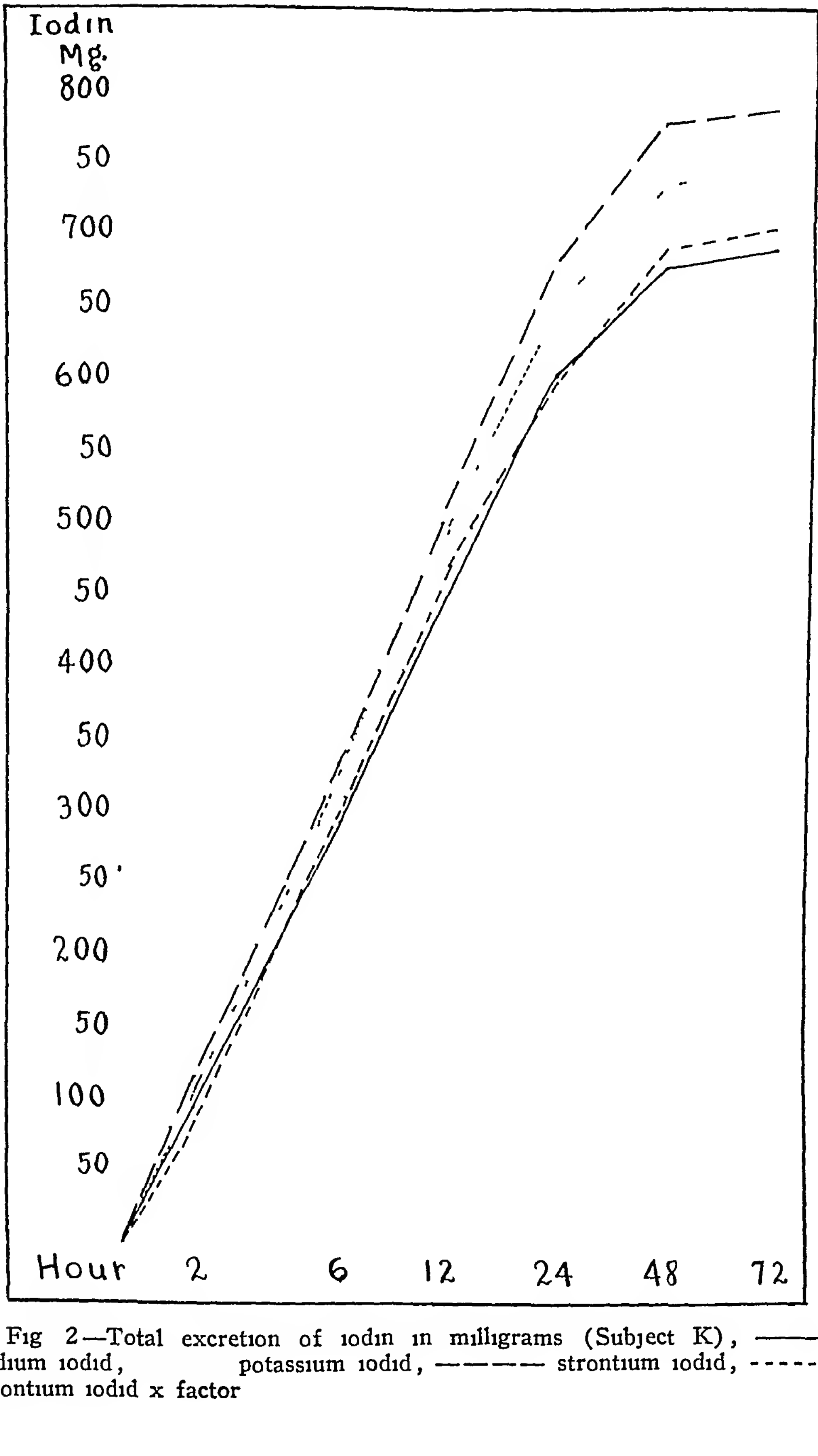

Fig 2—Total excretion of iodin in milligrams (Subject K), ——— sodium iodid, potassium iodid, — — — — strontium iodid, - - - - - - strontium iodid x factor

greater volume of urine was associated with a greater excretion of iodid, but the reverse was about as frequent The point is well illustrated in one instance of the potassium series in which the iodin excretion was strikingly uniform at the sixth hour period (225, 212 and 222 mg) with a marked variation in the urine output (600, 205 and 270 c c , respectively) The average volume of urine was practically the same with the different salts

Subjective Symptoms—About an hour after taking the iodid two subjects noticed an irritation or soreness of the pharynx which persisted for several hours and disappeared during the afternoon There was no apparent difference from the different iodids in the time of onset, intensity or duration of the symptoms No other symptoms were noted The third subject noted an acne eruption of the same degree from the strontium and sodium salts

CONCLUSIONS

The combination of iodin with strontium does not delay the excretion, and therefore the absorption, of iodin over that of sodium and potassium In fact, both the rate and total excretion seem to be slightly greater with the strontium iodid, although the difference seems immaterial

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HEART-BLOCK

II TRANSIENT COMPLETE HEART-BLOCK WITH NUMEROUS STOKES-ADAMS ATTACKS *

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AND

G CANBY ROBINSON, M D

ST LOUIS

Although syncopal attacks are fairly common in cases of complete heart-block, they do not, as a rule, occur with sufficient frequency in any given case to allow the cardiac mechanism during an attack to be graphically recorded Polygrams have been obtained during such attacks by Lewis,[1] and Williams[2] has obtained an electrocardiogram during an attack in one instance The following case is of interest because electrocardiographic records were obtained during several Stokes-Adams attacks, and also as an example of transient complete heart-block

REPORT OF CASE

History—Mrs N M, an American housewife, aged 48, entered the Barnes Hospital, May 10, 1917, on the advice of her family physician, Dr George Park She complained of fainting spells, vomiting and pain in the epigastrium and back The family history was unimportant She had had measles, mumps and a number of attacks of severe sore throat during childhood, but had been otherwise well until about ten years before, when she began to suffer from palpitation of the heart and slight dyspnea on exertion, both of which symptoms had continued up to the onset of the illness for which she entered the hospital She had never had a severe attack of cardiac decompensation She had had several attacks of severe pain in the epigastrium and back with fever and vomiting, and one such attack was accompanied by jaundice

Present Illness—About April 18, 1917, she became ill with pain in the epigastrium and back similar to that which she had experienced in previous attacks At this time she also had nausea and vomiting and some fever Her general condition remained about the same until the night of May 9 At about midnight of this date she became nauseated and asked for water Her husband went to procure this, and when he returned he found her unconscious Her pulse was weak and irregular A dash of cold water in the face revived her During the

* Submitted for publication Sept 1, 1917

* From the Department of Internal Medicine, Washington University Medical School

1 Lewis, T Lectures on the Heart, New York, Paul B Hoeber Company, 1915

2 Williams Personal communication

course of the night she had ten or twelve such attacks, and several more occurred during the next forenoon About 1 p m, May 10, 1917, she was brought to the hospital She was then having a syncopal attack every one or two minutes These attacks were described by the intern in charge about as follows Each attack was preceded by a cessation of the heart sounds and of the pulse, which did not return for from three to ten seconds Just before the pulse returned, after the longer pauses, the patient became cyanotic and very dyspneic, the eyes turned upward and she became unconscious At the end of the longer attacks there was some twitching of the extremities and occasionally of the whole body The heart sounds and the pulse then returnd, the patient quickly regained consciousness and the cyanosis and dyspnea disappeared

Physical Examination—Aside from these attacks the examination of the patient revealed little that was abnormal The cardiac dulness extended 3 cm to the right and 10 cm to the left of the midline On auscultation there was a systolic murmur, heard best along the left border of the sternum, but heard distinctly at the apex and transmitted into the axilla There was no edema of the ankles, ascites or hydrothorax The liver extended 3 cm below the costal margin and there was slight general abdominal tenderness The temperature reached 100 5 F on the day of admission, but was normal thereafter The remainder of the physical examination and the laboratory examinations, including the Wassermann reaction, were negative

GENERAL SURVEY OF THE GRAPHIC RECORDS

A general survey of the graphic records and the course of the patient's illness will be given first, after which the records will be described in detail The electrocardiograms taken May 10 shortly after the patient entered the hospital and while she was having syncopal attacks, revealed the presence of complete auriculo-ventricular dissociation with frequent periods of ventricular standstill lasting from seven to eleven seconds, and corresponding to the syncopal attacks About one-half hour later these periods of ventricular standstill began to be interrupted in the electrocardiograms by abnormal ventricular complexes, and at about the same time the syncopal attacks ceased During all of this time the ventricular rate between periods of ventricular standstill was approximately 90 per minute, while the auricles beat uninterruptedly at a rate of about 120 per minute About one hour after the first curves were taken, however, single normal ventricular complexes began to interrupt the periods of ventricular standstill and these periods became comparatively short One-half hour later the short periods of high ventricular rate with complete dissociation had disappeared and a partial heart-block of high grade was present

On the following day, May 11, complete dissociation returned for a time, but there were no periods of ventricular standstill and the complete dissociation quickly gave place to a 2 1 block The partial block then became gradually less marked until May 14, when the only sign of defective conduction which remained was a prolongation of the P-R interval which measured 0 31 second Thereafter, the improve-

ment in conduction was less rapid, but by May 25 the P-R interval had decreased to 0.20 second. During this time there was also a rapid improvement in the patient's general clinical condition.

The general picture, then, was one of complete dissociation with a rapid idioventricular rate and ventricular standstill causing Stokes-Adams syndrome. This was followed by improvement associated with a rapid decrease in the grade of the heart-block.

DETAILED DESCRIPTION OF THE GRAPHIC RECORDS

Figure 1 is an example of the electrocardiograms that were obtained at about 2 p. m. May 10, when the patient was having frequent syncopal attacks. It begins with a period of complete A-V dissociation during which the ventricular rate is 89.3 and the auricular rate 120 per minute. This period of complete dissociation is followed by a period of ventricular standstill lasting 9.06 seconds. During this period there is a gradual acceleration of the auricular rate, probably due to anemia of the vagus center, or possibly to the fall of blood pressure. The period of ventricular standstill is terminated by a period of complete dissociation exactly like that at the beginning of the figure. From the examination of a number of tracings similar to this one it became apparent that there was a fairly constant time interval between the first ventricular complex following a period of ventricular standstill and an auricular beat preceding it. This relationship was sufficiently constant to warrant the conclusion that the periods of ventricular standstill were terminated by an effective impulse passing from the auricles to the ventricles.

Figure 2 is an example of the electrocardiograms obtained about 3.00 p. m., May 10, at about the time that the syncopal attacks ceased. It is very similar to Figure 1, except that in it the long period of ventricular standstill was interrupted by the occurrence of ventricular contractions yielding complexes suggesting stimulus production within the left ventricle. The relationship of the first normal ventricular complex following the long pause to the preceding P wave is slightly but not markedly different from that seen in the previous figure. It will be noted in Figure 2 as well as in the other figures that the ventricular complexes following long periods of ventricular standstill differ somewhat in form from the others. This difference is partly due to the prolongation of the R-T time and is probably analogous to the changes in the form of the ventricular complex which occur as a result of changes in heart rate.

Records obtained shortly after Figure 2, show in addition to the abnormal ventricular complexes single normal ventricular complexes interrupting the period of ventricular standstill. These normal beats

bear the same relationship to the previous auricular beat as do the first ventricular beats after the long pauses.

Figure 3 is an example of the curves obtained shortly after Figure 2. The abnormal ventricular complexes no longer occur, but single normal ventricular complexes occur during the pauses at the rate of 1 for every 4 auricular beats, each ventricular complex bearing the same relationship to the preceding P wave as the first ventricular complex of a group. During the pauses 4:1 block is present, while during the periods of rapid ventricular rate there is complete dissociation.

Figure 4 is an example of the electrocardiograms obtained about 4:05 p. m., May 10. The groups of rapidly recurring ventricular beats no longer occur, and partial heart-block of high but somewhat mixed grade is now continuously present. Records obtained shortly after that shown in Figure 4 indicated a lower grade of partial block.

Figure 5 is an example of the curves obtained between 10:30 and 11 a. m., May 11. This figure shows a return of complete dissociation. The ventricular rate, however, is now only 66 per minute, instead of 90 per minute as on the previous day. Moreover, there are no periods of ventricular standstill. At this time the patient was given one-fiftieth grain of atropin sulphate hypodermically.

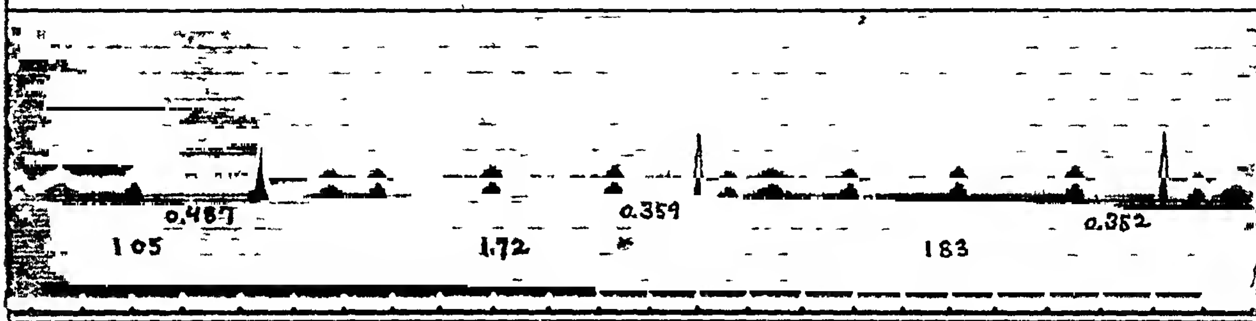
Figure 6 was obtained seven minutes after the atropin was injected. We see in this figure a 2:1 block with a ventricular rate of 56 as compared with 66 in the previous figure. This 2:1 block continued without change for the next hour. In view of the fact that it came on so soon after the administration of the atropin and that there was no change in the block during the next hour, it seems unlikely that the atropin was responsible for the disappearance of the complete block seen in the previous figure in favor of partial block. On the other hand we believe that this was due to the slowing of the idioventricular rate.

On the following day, May 12, the partial block was of still lower grade, a mixture of 3:2, and 4:3 rhythm.

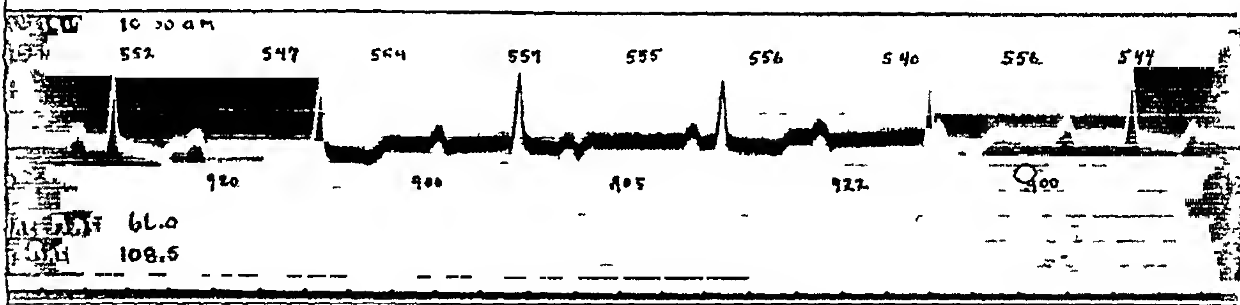
Figure 7 was taken at 10:45 a. m., May 14, four days after admission. Each auricular beat now produces a ventricular response, and the only sign of defective conduction is the prolongation of the P-R interval which measures from 0.310 to 0.315 second.

DISCUSSION

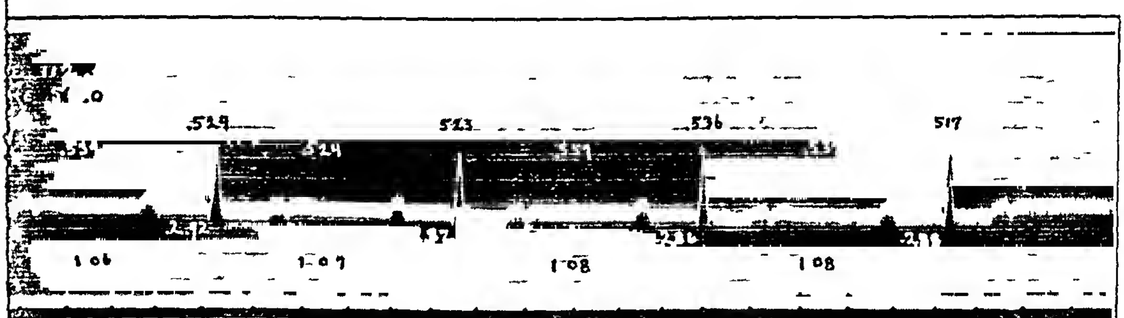
In discussing the cause of the periods of ventricular standstill and consequently of the syncopal attacks, we may first examine the tracings in the light of previous experience. Such periods of ventricular standstill are known to occur when complete heart-block is suddenly produced in the experimental animal, and also when a high grade of



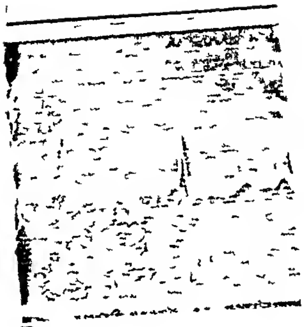
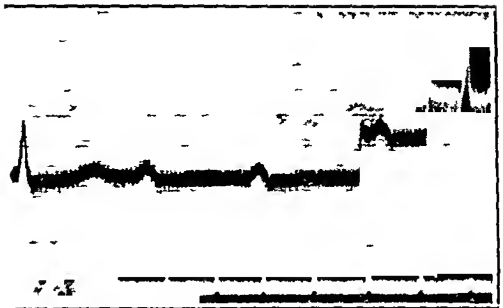
4—May 10, 4 05 p m Complete A-V dissociation no longer occurs It is replaced by partis

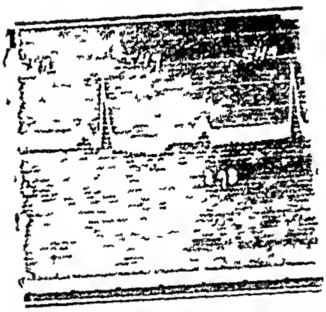


a m Complete A-V dissociation is again present The idioventricular rate is now 66 pe



eart-block, 2 1 rhythm Ventricular rate 56 per minute,



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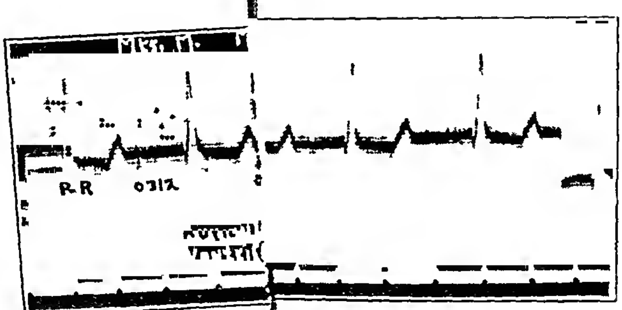

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Fig 7—May 12, 1[illegible]uricular beats are blocked

partial block suddenly becomes complete in man. In these instances ventricular stoppage is due, according to Erlanger and Hirschfelder,[3] to the slow development of the idioventricular rhythm. In our case, however, none of the above conditions were present; we are dealing with very numerous periods of ventricular standstill occurring while complete block was continuously present. Moreover, the ventricles did not develop their rhythm gradually at the end of a period of standstill but started in at full speed. In looking for unusual features which might explain the ventricular stoppage the attention is attracted by the unusually rapid idioventricular rate, which was about three times as fast as the usual idioventricular rate seen in complete heart-block. This seems to offer an analogy. The ventricular tachycardia in this case bears certain resemblances to a well recognized type of tachycardia, namely, paroxysmal tachycardia, which is characterized by the suddenness of its termination. In some cases of tachycardia there is perhaps a causal relationship between the successive beats of the paroxysm; each beat seems to be necessary for the production of the following beat. If for any reason any beat of the series fails to occur, the tachycardia comes to an end. Somewhat the same mechanism may be discerned during the periods of idioventricular tachycardia which occurred in our patient. Each period stopped suddenly without ascertainable cause.

The mechanism by which the ventricular stoppage was terminated became evident when a number of records were examined. It was found that the first ventricular beat following the long pauses bore a fairly constant relationship to a preceding auricular beat, indicating that these beats were sequential and that the ventricular stoppage was terminated because an impulse from the auricles reached the ventricles. The auricular impulse did not stimulate the ventricles, however, until the ventricular stoppage had continued sufficiently long to produce the conditions in the heart which were necessary for the effective passage of the impulse. In the later records, when conduction was somewhat improved, the periods of standstill were shorter.

It seems likely, therefore, that the ventricular stoppage was at least partly dependent on the abnormal character of the ventricular rhythm during the periods of ventricular tachycardia. The length of the periods of ventricular standstill was apparently determined by the time required for sufficient improvement in the auriculoventricular conductivity to allow an auricular stimulus to reach the ventricles; for, as the degree of block diminished the periods of ventricular standstill became shorter. The periods of standstill were apparently never long

3 Erlanger and Hirschfelder. Am. Jour. Physiol., 1905-1906, **15,** 153.

enough to allow the usual slow idioventricular rhythm to develop Three factors, then, took part in the production of the syncopal attacks the abnormal character of the ventricular rhythm, the high grade of heart-block, and the slow development of the idioventricular rhythm

The cessation of the syncopal attacks was apparently due to the occurrence of ventricular contractions arising in the left ventricle during the long ventricular pauses These beats, although they did not always occur after the elapse of exactly the same period of time following the occurrence of ventricular stoppage, were probably due to an impulse generated in one of the lower ventricular centers Had these beats failed to occur, however, the attacks would soon have ceased because of the rapid improvement in A-V conduction and the gradual disappearance of the tendency to ventricular tachycardia which are shown by the later records of May 10

The occurrence of a period of complete dissociation, May 11, appears to have been due to the recurrence of a ventricular rhythm of high rate This rhythm may or may not have been of the same character as that previously observed The ventricular rate was considerably slower and there was apparently no tendency to ventricular stoppage at this time This ventricular tachycardia disappeared rather suddenly after, but probably not as a result of, the administration of atropin, giving place to a 2 1 rhythm During the 2 1 rhythm the ventricular rate was considerably slower and it is possible that it was the rapid ventricular rate and not the condition of the junctional tissues alone which was responsible for the previous complete dissociation

Two explanations may be given for the occurrence of such a phenomenon The rapidly recurring ventricular beats may in some way depress the conductivity of the His bundle This idea is supported by the occurrence of prolonged P-R intervals after interpolated ventricular extrasystoles Erlanger,[4] however, has suggested a different explanation His view may be expressed as follows The irritability of the ventricles during the refractory period is zero, following the refractory phase the irritability of the ventricles increases according to a definite curve The height to which the curve of irritability rises depends on the form of the curve and on the duration of ventricular diastole The value of the threshold stimulus depends at any time, therefore, on the time which has elapsed since the previous ventricular beat and the rate of recovery of the ventricles When, because of the high rhythmicity of some ventricular center, the ventricles are driven at a rapid rate, the general ventricular irritability never reaches a high level It is conceivable that in such instances the stimuli from the auricles may fail to be effective on reaching the ventricles because they lie below the

4 Erlanger Personal communication

threshold value. When, as in the present case, the ventricular rate is relatively slow when compared with other types of tachycardia, this explanation is inadequate unless we further assume that the strength of the auricular stimuli reaching the ventricles is diminished by the defective A-V conduction, or that the increase in ventricular irritability is much less rapid than is usually the case. So far as we know, there is no exact experimental evidence bearing on this problem.

It remains to inquire into the etiology of the heart-block in our patient. The rapidity with which the block cleared up suggests that it was not due to some destructive lesion of the A-V bundle, but to some toxic or acute inflammatory process. The patient had received small doses of digitalis (5 drops of a proprietary preparation) for a period of about one week before entering the hospital, but it seemed unlikely that this small amount of the drug could have been responsible for the block unless the patient was especially susceptible to the digitalis bodies. To decide this point the tincture of digitalis was administered to the patient for a considerable period, beginning about two weeks after she entered the hospital. No marked changes in conduction were observed. The patient's history and the slight fever on the day of admission to the hospital indicate that she had recently had an acute infection, and it is possible that this was in some way responsible for the lesion which caused the block. The presence of an old endocarditis and possibly a chronic myocarditis indicated by the history and the presence of mitral regurgitation may have been a contributory factor.

SUMMARY

A case of transient complete heart-block is reported. When first observed the patient was having a great many syncopal attacks and the cardiac mechanism during some of these was recorded electrocardiographically. The attacks were caused by ventricular standstill lasting from seven to eleven seconds. The patient made a rapid clinical recovery, and at the same time there was a rapid decrease in the grade of block. The cause of the syncopal attacks and the etiology of the heart-block are discussed.

THE ENDOCRINE ORIGIN OF MUSCULAR DYSTROPHY *

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AND
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SCOPE OF THE PRESENT COMMUNICATION

Certain clinical and pathologic observations suggest that muscular dystrophy may originate as a result of dysfunction of the endocrine organs Such a view requires, however, the support of evidence of metabolic nature before it can be regarded as acceptable In the present investigation the metabolism in nine cases of muscular dystrophy was accordingly studied In addition to certain disturbances in the creatinin-creatin metabolism, there was observed constant hypoglycemia and impaired utilization of carbohydrate The metabolic picture presented is essentially the same as that recorded in the diseases of unquestionable endocrine origin (myxedema, hypopituitarism and Addison's disease) and after experimental removal of the thyroid or adrenal glands in animals In view of these metabolic findings, also the clinical as well as pathologic, it seems justifiable to regard muscular dystrophy a result of dysfunction of the ductless glands

CLINICAL MATERIAL

This was selected from the neurologic wards of the Montefiore Hospital, and consisted of a representative series of muscular dystrophy cases, including both light and severe, in children and adults Our patients well exemplify the fact that muscular dystrophy is a distinctly familial disease, for eight of our nine patients gave such a history The greater tendency of males to become affected is shown by the fact that eight patients were men or boys Practically all gave evidence of trophic changes in the nails, skin, hair, etc A peculiar distribution of hairy areas was observed in three cases Pigment deposits, osseous changes, etc , were also found

Roentgenologic studies were made in each instance The results are very instructive Aside from Case 1 in which the findings were negative, the entire series showed rarefaction of the skull and long bones, in some cases underdevelopment, in two cases pineal shadows

* Submitted for publication Sept 18, 1917
* From the Montefiore Hospital

The osseous system is evidently almost as frequently affected as is the muscular, as will be observed by reference to the accompanying roentgenograms Case 9 showed acromegalic changes Abstracts of the patients' histories follow The cases are arranged throughout the article in the order of their severity

REPORT OF CASES

Case 1—Joseph G, a boy, aged 11 years, had one sister who was affected with muscular dystrophy He was operated on four years previously for cataracts of both eyes His present illness began at the fourth year with distinct progressive weakness in all the muscles of the body There is at present general muscular wasting and weakness with the exception of the calf muscles

Fig 1 (Case 1)—Showing general muscular wasting, "winged" scapulae, and the characteristic manner of rising from recumbent position

which are in a condition of pseudohypertrophy When lying on the floor the patient assumes the erect position in a characteristic manner by rising on one knee, extending the other leg, pulling himself up on that and then dragging up the other leg (Fig 1) There is a myotonic reaction in the tongue, thenar and hypothenar eminences and the deep reflexes are but feebly elicited When walking the patient has a characteristic steppage gait On appropriate movements there are typical winged scapulæ The facies is of the myopathic type and there is very little fatty tissue There are hirsutes on the extensive surface of the upper extremities just above and below the elbow Marked cyanosis is present in the peripheral portions of all four extremities which is only slightly influenced by posture, the hands remaining distinctly cyanosed even when elevated The Wassermann reaction is negative

The roentgenographic examination of the skull and long bones was essentially negative

Case 2—H S, a woman, aged 43 One brother died at the forty-fifth year of progressive muscular dystrophy The onset of the disease began in her thirty-eighth year with weakness in the lower extremities, and upper extremities in lesser degree Motor paresis in neck muscles developed later Present status Facies characteristic of primary myopathy (Fig 2), motor power markedly diminished, intense cyanosis of feet, volume of musculature is lost throughout the body, with far greater relative diminution of function, gait slow and hesitating, with broad base, wasting of muscles of neck and shoulders, sternocleido-

Fig 2 (Case 2)—Facies characteristic of primary myopathy

mastoids atrophic, myotonic reaction in muscles of tongue and right thenar and hypothenar eminences The patient is unable to raise herself on the chair without assistance, and she has a low monotonous speech

The roentgenographic examination shows small spots of bone absorption scattered throughout the upper portion of the cranium There is a faint shadow, about 5 by 7 mm situated slightly above and 3 5 cm posterior to the tip of the posterior clinoid process This shadow suggests the pineal gland

Case 3—N B, a man, aged 42, has two brothers known to have muscular dystrophy The patient lived under unhygienic conditions, his work exposing him to metallic dust of lead, brass, antimony, etc The onset began at the twenty-sixth year, was gradual, with progressive weakness in right arm, extending to left, then involving both lower extremities There is marked exoph-

thalmos and dilated pupils (Fig 3) The patient cannot assume a sitting posture but maintains it when assisted The head is flexed and rotated to the right There is marked atrophy of the sternocleidomastoids, trapezii and muscles of the forearms The deep reflexes are absent (knee jerks diminished) The characteristics in this case are contrasted pseudohypertrophy and weakness of function of the calf muscles The muscle tissue seems to be replaced almost entirely by fat The Wassermann reaction is negative

The roentgenographic examination shows very marked bone rarefaction in the skull, evidently in the tabula interna, simulating strongly the convolutions of the brain The extremities show moderate diffuse bone rarefaction, somewhat more marked in the lower In both tibiae there is evidence of very advanced localized bone absorption running in the form of two narrow strips throughout the upper half of the diaphysis, suggesting cavity formation (Fig 4)

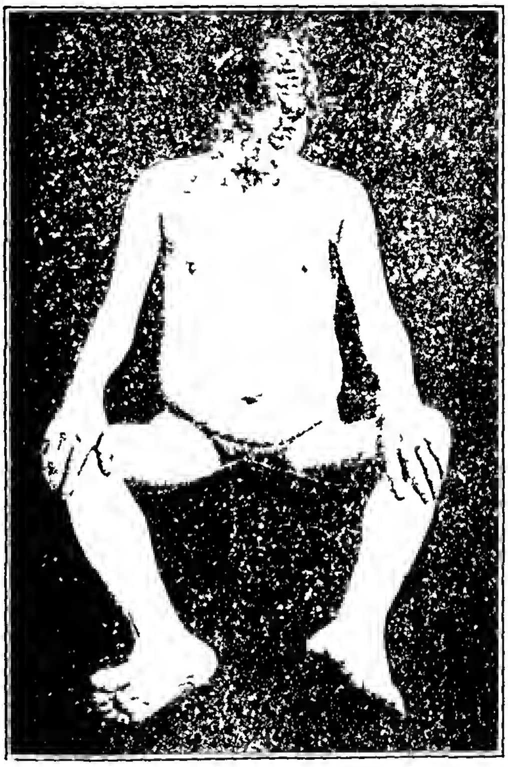

Fig 3 (Case 3) —Muscular dystrophy with marked exophthalmos

Case 4—L S, a man aged 48, has two brothers who are affected with primary myopathy At the thirtieth year in our patient weakness began in both upper and lower extremities (Fig 5) He is able to move about only in a wheelchair, and has difficulty in assuming a sitting position There is flexion of both thighs and knees and contraction of the hamstring muscles Extension of legs is limited to 130 degrees His body is of wasp-like contour, facies myopathic, and the calf muscles are weak with the characteristic sclerotic feel Pseudohypertrophy is present There is marked wasting of the general musculature The deep reflexes cannot be elicited because of atrophy Electrical examination shows quantitative changes in the affected muscles The skin is cold and clammy, the feet cold and cyanotic and there are trophic changes in the nails The pulse is slow and of low tension

Roentgenographic examination shows several small irregular spots of bone absorption scattered throughout the parietals and frontals (Fig 6) There is an irregular shadow, about 0 5 to 1 cm on the level of and 4 cm posterior to the tip of the posterior clinoid process (pineal body?) Evidence of bone

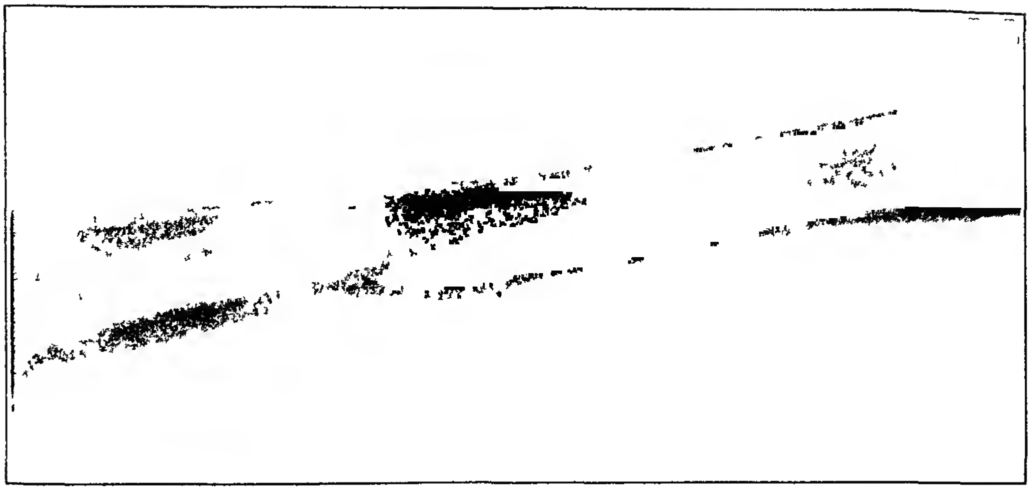

Fig 4 (Case 3) —Evidence of localized bone absorption in the tibia The narrow strips of bone throughout the upper half of the diaphysis suggest cavity formation

Fig 5 (Case 4) —General muscular dystrophy with pseudohypertrophy of calf muscles

absorption of the posterior clinoid process is present, the sella turcica is not enlarged, and there is marked, diffuse bone atrophy in the upper extremities In some places differentiation between compacta and spongiosa has entirely disappeared There is a moderate amount of diffuse atrophy of all bones of the lower extremity, including tarsal bones

CASE 5—L K, aged 19, has two brothers who are affected with progressive muscular dystrophy There is an extra digit on all four extremities (congenital deformity) The onset began at the third year with progressive weakness, in the order named of the lower extremities, upper, back, and facial musculature (Fig 7) The calf muscles show the usual pseudohypertrophy with

Fig 6 (Case 4)—Small irregular spots of bone absorption throughout the parietal and frontal bones The irregular shadow toward which the arrow points at the anatomic location of the pineal body would seem to indicate an enlarged organ

the characteristic sclerotic feel The whole skeletal structure appears stunted, the long bones between the knees and the ankle are abnormally short, and there is a peculiar distribution of the hirsutes, the individual hairs being abnormally long, especially about the groins and thighs anteriorly

The roentgenographic examination shows underdevelopment of the long bones and absorption of osseous tissue

CASE 6—H B, aged 18 years His father is an epileptic, and he has two brothers affected with muscular dystrophy One maternal aunt is insane

The onset began at the fifth year with generalized muscular weakness and slowly progressive wasting The calf musccles show typical pseudohypertrophy (Fig 8), and the orbicularis oris and palpebrarum muscles are atrophic The trunk deformities are in large part due to muscle wasting The hair is strikingly long and abnormally distributed, scalp hair very dry and brittle and there are trophic ulcers on the fingers and toes

The roentgenographic examination shows marked, diffuse rarefaction of all bones examined They are abnormally thin and underdeveloped (Fig 9)

Case 7—James G, a boy, aged 15 There is profound muscular weakness with contractures involving almost the entire musculature of the limbs and trunk The sternocleidomastoids are atrophied and there is extreme distortion

Fig 7 (Case 5)—Whole skeletal structure appears to be stunted, pseudohypertrophy of calf muscles, long bones between knees and ankles abnormally short, peculiar distribution of hirsutes

of the trunk (Fig 10) This case represents an advanced muscular degeneration The facial muscles on both sides are involved in the typical myopathic loss of function on effort The exophthalmos is emphasized by the partial wasting of the orbiculares palpebrarum There is marked dryness of the skin on the abdomen and a deposition of brown pigment The teeth are wide apart, and there is macroglossia

The roentgenographic examination shows marked underdevelopment and rarefaction of all bones examined, most advanced in the carpus and tarsus

Case 8—M E, aged 19 years, has one brother affected with muscular dystrophy At the third year the patient's manner of gaining the erect position typical of muscular dystrophy was observed He was never able to run and

climb stairs There is marked wasting of all muscles of the body and contractures in the hamstrings and calf muscles (Fig 11) The enlargement of the calf muscles and the peculiar sclerotic feel are in contrast to the marked general atrophy elsewhere The skin is peculiarly dry, with diffuse areas of brownish pigmentation and a prolific long hairy growth about the pelvis and thighs The cyanosis of the lower extremities in the distal portions is marked and there is a tendency of the soft parts to ulceration

The roentgenographic examination shows atrophy of all bones examined The lower portions of ulnae and radii are abnormally thin from underdevelopment

Fig 8 (Case 6) —Deformities of trunk due in large part to muscle wasting; pseudohypertrophy of calf muscles, atrophic condition of orbicularis oris and palpebrarum muscles, abnormal distribution of hair, trophic ulcers on fingers and toes

Case 9—I R, boy, aged 14 years, gives a family history which contains no element relevant to the patient's condition The initial symptoms bearing on the development of the muscular dystrophy date from the boy's third year The patient gave the history of gradual weakness beginning in the lower extremities, progressively involving girdle, facial and shoulder musculature (Fig 12) Pseudohypertrophy and atrophy have finally reached a very high degree There is also, in part secondary to the marked involvement of the trunk muscles, extensive kyphoscoliosis from sixth dorsal to midsacral region The general massive bony contour of the head and face, and especially the marked prognathic lower maxilla, are decidedly of the acromegalic cast The sexual development, in contradistinction to the other cases reported, shows abnormally advanced maturity of growth (Fig 13) There is marked macro-

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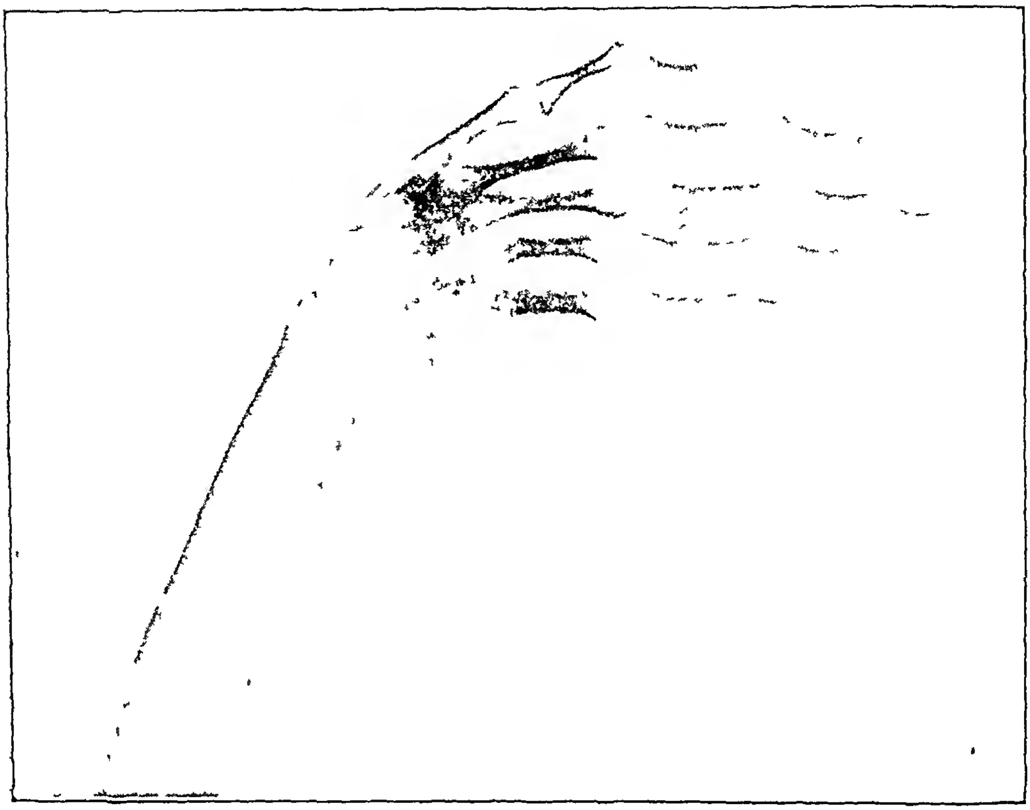

Fig 9 (Case 6) —Showing marked rarefaction and underdevelopment in the bones of the hand and forearm This diffuse rarefaction was present in all of the bones examined

Fig 10 (Case 7) —Profound muscular weakness with contractures involving almost the entire musculature of the limbs and trunk, extreme distortion of trunk, typical myopathic loss of function of facial muscles, etc

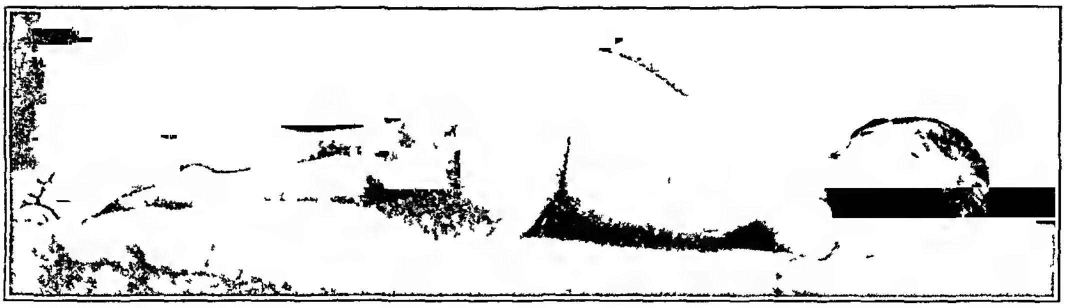

Fig 11 (Case 8) —Marked wasting of all the muscles of the body and contractures in the hamstrings and calf muscles

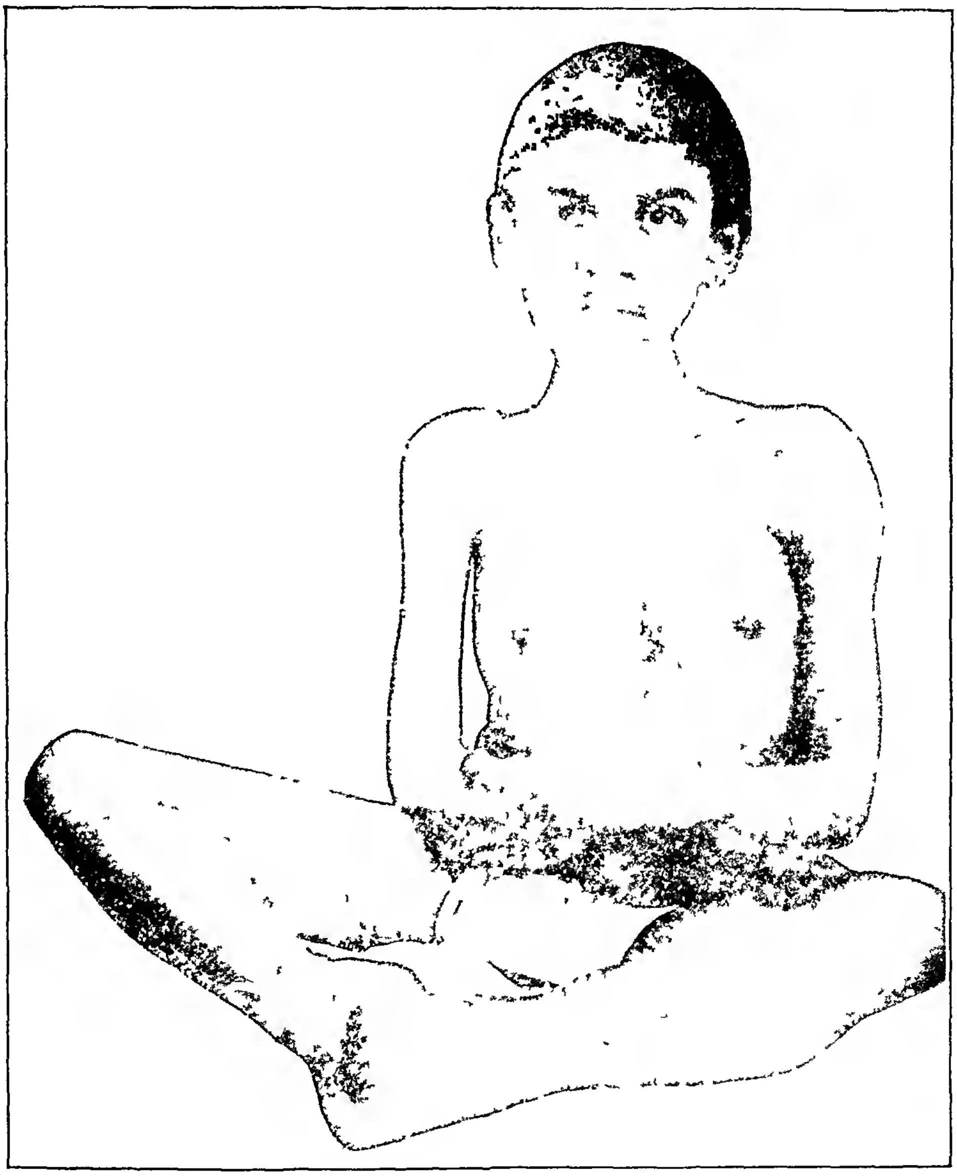

Fig 12 (Case 9) —Marked involvement of trunk muscles, extensive kyphoscoliosis from sixth dorsal to midsacral region, general massive contour of head and face, prognathic lower maxilla, decided acromegalic cast, excessive growth of hair over body

glossia, the tongue in protrusion being really huge (Fig 14) There is excessive hair growth over the entire body

Roentgenographic study of the skeleton structure examined, shows the usual underdevelopment of the long bones Those of the skull, especially the lower jaw, present markedly acromegalic features

METHODS OF INVESTIGATION

In general the methods employed were those described in previous articles by one of us The advantages of a metabolism ward were utilized in this study The cases were segregated under constant supervision in separate rooms, and cared for by night and day nurses trained in metabolism studies A special diet kitchen was used The diet was creatin-creatinin free, was kept uniform during the experimental periods, and in all cases was weighed Representative articles of food used were bread, butter, eggs, milk, potatoes, rice, pears, custard, sweet corn, orange, and lettuce, the amounts taken varying somewhat with

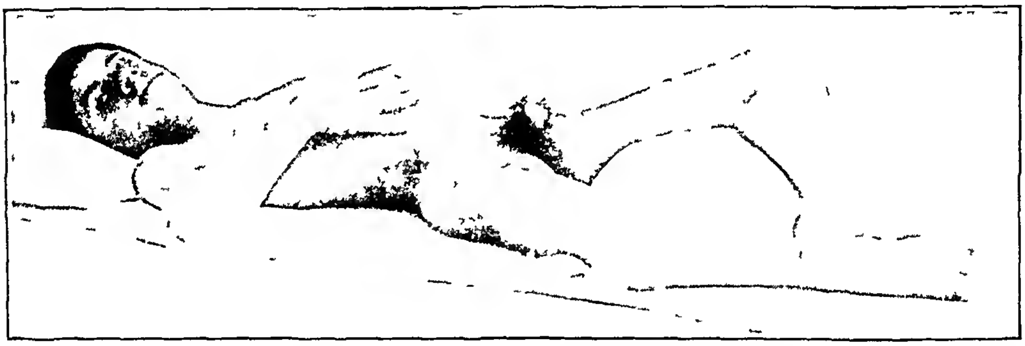

Fig 13 (Case 9) —The underdevelopment of the long bones with contrasted acromegalia of the bones of the skull, especially the inferior maxilla, is very marked in this case

the clinical condition and age of the patients Those undergoing study were placed on the diet four to seven days before the beginning of the experimental period, as recorded in the protocols The urine was collected in twenty-four-hour periods with proper precautions In the cases of three patients who were helpless cripples it was found impossible sharply to demarcate the twenty-four-hour periods, and this fact is noted in the protocols

The metabolic studies consisted in the determination of the endogenous creatinin-creatin metabolism, total nitrogen, blood sugar and blood sugar tolerance curves It is fully recognized that these phases of metabolism are partial only and should be supplemented by others such as the purin and mineral exchange As the work was undertaken for the purpose of determining the nature rather than extent of the metabolic disturbances, and the labor involved in this investigation of nine cases is very considerable, a study of the calcium and magnesium metabolism was made only in one instance

Fig 14 (Case 9) —Extreme macroglossia in a boy aged 14 In this case there was an excessive hair growth over the entire body

TABLE 1—Dietary Data

Case Number	Nitrogen in Food	Calories in Food	Calories per Kilogram of Body Weight
1	9 03	1,275	55
2	9 38	1,765	30
3	11 11	1,895	31
4	9 38	1,765	38
5	11 11	1,895	56
6	9 03	1,275	48
7	9 03	1,275	53
8	9 03	1,275	39
9	9 03	1,275	31

TABLE 2—PROTOCOLS OF URINARY ANALYSES

Case	Days	Volume, C c	Total Nitrogen, Gm	Creatinin, Gm	Creatin, Gm	Creatin Plus Creatinin as Creatinin, Gm
1	1	180	2 80	0 167	0 066	0 212
	2	340	3 94	0 151	0 176	0 303
	3	440	6 74	0 128	0 317	0 402*
	4	220	3 59	0 197	0 140	0 317†
2	1	720	5 21	0 279	0 210	0 461
	2	920	7 18	0 317	0 375	0 641†
	3	660	7 62	0 365	0 208	0 544*
3	1	440	6 84	0 209	0 622	0 745
	2	480	6 62	0 213	0 638	0 763
	3	540	7 20	0 211	0 604	0 732
4	1	540	7 53	0 254	0 660	0 832*
	2	450	5 61	0 198	0 538	0 662†
	3	440	5 25	0 209	0 592	0 719
5	1	480	8 47	0 128	0 621	0 663
	2	540	7 51	0 135	0 610	0 661
	3	720	7 96	0 136	0 598	0 651
6	1	1,040	6 18	0 104	0 578	0 602
	2	1,020	6 35	0 108	0 577	0 606
	3	680	6 42	0 089	0 530	0 546
7	1	660	4 99	0 102	0 404	0 460
	2	790	8 86	0 100	0 654	0 664
	3	680	7 91	0 122	0 518	0 569
8	1	420	7 11	0 086	0 230	0 284
	2	650	6 03	0 101	0 145	0 223
	3	590	3 95	0 079	0 140	0 200
9	1	850	8 35	0 160	0 617	0 691
	2	930	11 18	0 190	0 708	0 800
	3	610	7 83	0 146	0 583	0 649

* Slightly more than twenty four hours

† Slightly less than twenty four hours Sum of these two days, however, equals forty eight hours

TABLE 3.—Urinary Creatinin and Creatin Per Kilogram of Body Weight *

Case	Creatinin, Mg	Creatin, Mg	Case	Creatinin, Mg	Creatin, Mg
1	6.8	7.5	6	4.2	23.0
2	5.2	4.3	7	4.0	19.5
3	3.4	10.0	8	2.8	5.4
4	4.7	12.8	9	4.1	15.9
5	3.9	17.9			

* Average of three twenty four hour periods in all cases except Case 1, which is a four day average

TABLE 4.—Blood Analyses Milligrams Per 100 C.c.

Case	Creatinin	Creatin	Urea Nitrogen
1	0.52	6.8	18.7
2	0.45	5.8	
3	0.48	11.3	18.5
4	0.27	10.8	
5	0.55	6.9	
6	0.36	7.1	21.6
7	0.43	6.9	
8	0.48	6.6	8.9
9	0.28	7.2	22.4

ANALYTIC METHODS

Urine

Creatinin according to Folin [1]
Creatin according to Benedict [2]
Glucose according to Pavy-Kumagawa [3]
Calcium and magnesium according to McCrudden [4]

Feces

Calcium and magnesium according to McCrudden [4]

Blood

Urea nitrogen according to Van Slyke and Cullen [5]
Creatinin according to Folin [6]
Creatin according to Benedict and Myers [7]
Blood sugar according to Epstein's modification of Lewis and Benedict's method [8]

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1 Folin, O Ztschr f physiol Chem, 1904, **41,** 222
2 Benedict, S R Jour Biol Chem, 1914, **18,** 191
3 Analyse des Harns, Neubauer-Huppert, 1910, **1,** 399
4 McCrudden, F H Jour Biol Chem, 1911, **10,** 187
5 Van Slyke, D D, and Cullen, G E Jour Biol Chem 1914, **19,** 211
6 Folin, O Jour Biol Chem, 1916, **28,** 349
7 Benedict, F G, and Myers, V C Am Jour Physiol, 1907, **18,** 397
8 Epstein, A A Jour Am Med Assn, 1914, **63,** 1667

EXPERIMENTAL RESULTS

The daily protocols of the urinary findings are grouped in Table 2 In contradistinction to the results of many metabolic studies on patients those obtained in this series of nine cases are definite and uniform throughout They all show certain abnormalities in the creatinin-creatin and carbohydrate metabolism, as is emphasized in the following summary of our findings

SUMMARY OF EXPERIMENTAL RESULTS

1 Marked decrease in the preformed creatinin in the urine
2 Abnormal presence of creatin in the urine
3 Low values of creatinin in the blood
4 Normal amount of creatin in the blood
5 Hypoglycemia
6 Delayed glucose utilization (hourly blood sugar curve)

DETAILED RESULTS

Urinary Creatinin The creatinin excretion showed its well known tendency to bear no definite relation to the total nitrogen excretion Normally, about from 17 to 22 mg of creatinin per kilogram body weight is excreted on a creatinin-creatin-free diet As is evident from Table 3, only one-sixth to one-third of the usual amount was found in our series Although reduced in all cases, the amount present seems to bear a certain relation to the severity of the clinical symptoms for the creatinin was usually decreased more in the severer than in the lighter cases

Urinary Creatin Moderate amounts of this abnormal constituent of human urine were present in each case The amount of creatin excreted in eight of the nine cases exceeded the creatinin

Blood Creatinin The values obtained by us vary from 0 27 mg to 0 55 mg of creatinin per 100 c c of blood If the normal value is from 1 to 2 mg per 100 c c, as has been generally accepted, the blood creatinin of our muscular dystrophy cases is distinctly low Unfortunately, the accuracy of blood creatinin determinations is still open to some criticism,[9] and may be found to be normally lower than is generally supposed We therefore prefer at present not to draw definite conclusions from these observations The apparently low values may, however, bear a relation to the low level of the urinary creatinin The sum of creatinin plus creatin is generally below normal

Blood Creatin This was found to range nearly within normal limits in every case It is to be remarked that the appearance of creatin

9 Gettler, A O Jour Biol Chem, 1917, **29**, 47

in the urine was unaccompanied by an increase in the creatin of the blood

Blood Glucose A definite hypoglycemia was demonstrated in our cases The blood was examined in the morning before breakfast in order to avoid the influence of food Repeated examinations showed the blood sugar to remain constantly at a low level Although low blood sugar values are observed at times under those conditions in normal persons, such observations are infrequent and inconstant

Carbohydrate utilization has been observed in our laboratory for some time According to an unreported study the administration of 1 75 gm of glucose per kilogram of body weight in 40 per cent solution causes a characteristic rise in the blood sugar of normal individuals, the fasting blood sugar level being reattained one and one-half to two hours after ingestion In possession of these data it was deemed advisable to make similar examinations in our dystrophy cases

TABLE 5—Blood and Urine Examination for Carbohydrate Assimilation

Case	Blood Glucose in per Cent						Urinary Glucose Twenty Four Hours Gm
	Fasting	After Glucose Ingestion					
		1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	
1	0 086	0 110	0 083				Negative
2	0 065	0 146	0 156	0 117	0 078		Trace
3	0 070	0 110	0 096	0 082	0 071		2 5
4	0 080	0 198	0 196	0 0	0 127	0 062	3 7
5	0 067	0 113	0 069				Trace
6	0 080		0 115	0 096	0 083		0 27
7	0 085	0 123	0 080				Negative
8	0 073	0 131	0 192	0 077			Negative
9	0 068	0 127	0 095	0 090	0 063		Negative

The results of these studies appear in Table 5 In each case the blood sugar was determined in the morning after a night's fast This was followed by the ingestion of 1 75 gm of glucose per kilogram in 40 per cent solution Blood sugar estimations were then made at hourly intervals The results of these examinations bring out the fact that there is a distinct delay in the disappearance of carbohydrate from the blood of five out of nine cases, the normal blood sugar value not being reattained until the end of the fourth or fifth hour after glucose ingestion instead of previous to the end of the second hour, which is the rule in normal subjects

It is interesting to observe that we are here probably dealing with a real defect in the proper removal of glucose from the blood, as will

now be explained After ingestion of the measured amount of glucose the highest point of the resulting rise in the blood sugar represented a large percentile increase over the fasting blood sugar level This increase amounted to about 65 per cent on an average of the fasting value, whereas the normal rise is only about 20 per cent under precisely the same conditions As would be expected in view of the hypoglycemia, the absolute sugar values are not generally elevated more than in normal subjects undergoing the tolerance test[10]

The significance of these findings will be discussed later The definite presence of glycosuria following the sugar ingestion in five out of nine cases is another sign of the inability of these patients to assimilate carbohydrates in the usual manner, for normal persons rarely react with glycosuria after the ingestion of sugar in the amount given here

The total urinary nitrogen excretion was low in all cases Complete nitrogen balances were not attempted, but judging from a comparison of the nitrogen of the food taken to that of the urine, there is an evident tendency to retention of nitrogen This was unexpected, as the creatinin-creatin-free diet was low in nitrogen

Blood urea nitrogen determinations were made as a check in five cases and found to present no striking deviations from the normal

TABLE 6—Calcium and Magnesium Exchange, Case 9

	Day	Intake, Gm	Output		Balance, Gm
			Urine, Gm	Feces, Gm	
Calcium oxid	1	1 83	0 14	0 35	1 34
	2	1 83	0 10	0 35	1 38
	3	1 83	0 12	0 35	1 36
Magnesium oxid	1	0 53	0 04	0 14	0 35
	2	0 53	0 03	0 14	0 36
	3	0 53	0 06	0 14	0 33

The calcium and magnesium exchange was studied over a short period in Case 9 The feces were demarcated with carmin at the beginning and end of the experimental period and the daily excretion averaged from the total obtained The urine was analyzed daily A large retention of both calcium and magnesium is evident from Table 6, in which the results are collected On a diet containing an adequate

10 Case 4 showed glycosuria on a normal diet and is to be regarded as complicated with a tendency to diabetes The blood sugar values are accordingly omitted in obtaining the average percentile increase in the tolerance test

amount of calcium, it was found that the calcium and magnesium output in both urine and feces, as well as their total excretion, was quite small A large retention of these mineral elements was evidently taking place here Whether a low calcium and magnesium output is a constant feature in muscular dystrophy is a question open for future decision by means of extended metabolic studies

DISCUSSION

Creatinin-Creatin Metabolism —Though we are still far from adequately understanding the metabolism of these substances, a definite connection between them and the muscle metabolism is fairly well established The well known occurrence of considerable amounts of creatin in muscle and other facts of more purely scientific interest support this view This matter has also been the subject of considerable clinical study In reviewing such results one must bear in mind that in some instances only the total creatinin, that is, creatinin plus creatin has been followed Thus Pemberton[11] has reported a case of myasthenia gravis with a total creatinin output of 0 59 gm daily, namely, a reduced excretion Such examinations of the urine are not very instructive for they fail to differentiate between creatinin and creatin This is important, as these substances have such strikingly different fates in the organism Thus, Janney[12] administered a large dose of Kendall's thyroid hormone to a fasting dog There resulted the clinical picture of hyperthyroidism accompanied by an enormous breakdown of body tissue and rise in total nitrogen and purin metabolism, also the appearance of creatin in considerable amounts in the urine The creatinin, however, remained utterly unchanged in spite of the hyperpyrexia and other toxic symptoms present We are thus forced to accept that different factors may control the metabolism of creatinin and creatin, as Folin first pointed out Shaffer[13] in an important study which should be better known clinically, came to the conclusion that the urinary creatinin was a measure of the muscular efficiency of the patient This view receives a certain substantiation in the fact that in various states of muscular weakness, the creatinin excretion is decidedly lowered Such are exophthalmic goiter, myasthenia gravis, myotonia congenita and muscular dystrophy For the last disease, Spriggs,[14] Levene and Kristeller[15] and the present writers

11 Pemberton, R Am Jour Med Sc, 1910, **139,** 816
12 Article in course of preparation
13 Shaffer, P A Am Jour Physiol, 1908, **23,** 1
14 Spriggs, E I Biochem Jour, 1907, **2,** 206
15 Levene, P A, and Kristeller, L Am Jour Physiol, 1909, **24,** 45

report low creatinin values McCrudden and Sargent's[16] case is exceptional in this respect, since in that case normal values for creatinin were found

The blood creatinin in muscular dystrophy has been previously little studied McCrudden and Sargent report normal values in their single case In view of the low urinary values found in our series of nine cases, one would expect low blood creatinin values, which we actually did find, but accept only with reservation as previously explained

The appearance of creatin in human urine if the diet is creatin-free is pathologic Creatin is excreted in conditions involving active-muscle breakdown Thus, it has been observed in toxic and febrile states, in muscular diseases, and in inanition During uterine involution the greatest amounts have been reported[17] There seems little doubt of its constant presence when sought for in muscular dystrophy Levene and Kristeller detected it in five cases, we in every case studied Blood creatin in McCrudden and Sargent's case and our own cases presented no striking abnormalities In our cases the total urinary creatinin plus creatin was reduced Our normal values for creatin in the blood do not therefore exclude the possibility of a *relative* increase of blood creatin

The carbohydrate metabolism in muscular dystrophy has been hitherto studied only in isolated instances McCrudden and Sargent's observation of hypoglycemia in a single case has been later corroborated by them in other cases[18] Our observations have been alluded to That the metabolism of carbohydrate is actually delayed is shown by the tolerance tests

Evidence Indicative of the Endocrine Nature of Muscular Dystrophy—(*a*) *Pathologic and Clinical*—In attempting to coordinate the complex manifestations of this interesting and relatively rare disease, the older point of view that it is limited to the muscle obviously must be abandoned A purely nervous origin of muscular dystrophy can also be excluded, as lesions of the central or peripheral neurons are not recorded in the great majority of cases In view of the articular, osseous and tendon changes reported by various observers, it is indeed evident that muscular dystrophy has a more general pathology

We may now discuss the osseous changes These were present in nearly all our series It is very probable that if roentgenographic studies were regularly made in such cases, increased numbers would

16 McCrudden, F H, and Sargent, C S The Archives Int Med, 1916, **17,** 465

17 See Footnote 13

18 Verbal communication to the authors

show the bony changes to be rather constant The osseous lesions have been usually ascribed to atrophy from disuse It is very questionable, however, whether this is the true explanation Thus Tixier and Roederer[19] report four cases of muscular dystrophy exhibiting, aside from myopathy, osseous changes resembling osteomalacia and dwarfism Three of the cases having this significant syndrome were children of the same parents This type of osteodystrophy was first described by Hutinel[20] in 1911 Hahn[21] likewise points out that the bone changes are not those of disuse

Sterling[22] reports a significant and instructive case of simultaneous osseous changes and muscular dystrophy The case is not definitely classifiable The osseous changes in this instance are worthy of note and were specially studied The muscle atrophy affected both upper and lower extremities, was primary, and appears to have been a dystrophy The patient was a healthy boy of 17 with negative heredity The malady developed gradually, beginning two years before admission with paresis and atrophy of the lower limbs Pain in the knee joints appeared three months later, followed about a year later by objective osseous changes in the knee and ankle joints A year subsequently the upper extremities became similarly affected, with elbow and wrist joints and deformity of the thorax and spinal column Roentgen-ray examination showed decalcification of the epiphyses and to a lesser extent of the diaphyses The osseous enlargements in this case were found to be due to separations which passed transversely through the bone, causing wide gaps in tissue, and in which a reconstructive callous formation of osteoid nature was found Microscopically, the pathologic process suggested osteomalacia Clinically, the bone changes are those seen in the course of exophthalmic goiter as described by von Jaksch and Rotky [23]

Von Jaksch and Rotky's observation is pertinent and worthy of direct reference The patient described by these authors was a young woman of 20 who had symptoms of exophthalmic goiter and in whom the superior and inferior thyroid arteries were ligated After temporary recession of symptoms for two years, painful enlargements appeared at the distal portions of the bones of both forearms, with similar osseous changes in the bones of the legs and the pelvis The thorax became deformed as a result of kyphoscoliosis There was exquisite tenderness of the entire skeletal structure Roentgenograms

19 Tixier, L, and Roederer, C Presse méd, 1913, **21,** 95
20 Hutinel, V Gaz d hop 1912, **85,** 27
21 Hahn, F Ztschr f Nervenh, 1901, **20,** 137
22 Sterling, W Ztschr f d ges Neurol u Psychiat, 1913, **19,** 241
23 Von Jaksch, R, and Rotky, H Festschr a d Geb d Roentgenstrahlen 1908-1909, **13,** 1

Other factors may, however, play a rôle in the production of these phlorizin poisoning symptoms

Our contention that the ultimate origin of muscular dystrophy lies in an endocrine dystrophy is further strongly supported by clinical and experimental analogies, which will now be detailed Practically all the clinical symptoms and metabolic signs already referred to have been observed in well known hypofunctional conditions of the ductless glands

Hypoglycemia in Other Endocrine Conditions —In myxedema, Geyelin[28] has reported hypoglycemia In cretinism we have observed hypoglycemia accompanied by creatin in the urine A delay in carbohydrate utilization in a creatin and several exophthalmic goiter patients studied by us was demonstrated by blood sugar curves[29] Cushing[30] called attention to hypoglycemia in dyspituitarism It has also been observed in Addison's disease[31] Muscular asthenia is not necessarily accompanied by a low blood sugar value Thus, in diabetes and some cases of exophthalmic goiter, hyperglycemia and muscular weakness coexist The causes of the hyperglycemia in these diseases are, however, different In diabetes it is probably due to inability to oxidize and synthetically utilize carbohydrate, while in exophthalmic goiter the increased blood sugar may be the result of toxic breakdown of protein characteristic of this disease

Hypoglycemia Not Due to Disuse —If hypoglycemia is a characteristic of deficient endocrine function and is not the result of a lessened requirement for carbohydrate due to smaller quantities of muscle tissue to be nourished, one should not expect to observe it in chronic arthritis cases McCrudden and Sargent, who very properly raise this point, accordingly made blood sugar determinations in several of such cases and found normal values We have extended these control studies to five similar cases with secondary generalized muscle atrophy and have likewise found the blood glucose at or slightly above its normal level The values obtained by us were as follows

Case, W M, arthritis deformans, 0 102 per cent, 0 104 per cent Case, M R, chronic polyarthritis, 0 122 per cent, 0 124 per cent Case, M S, arthritis deformans, 0 107 per cent Case, M L, chronic infectious polyarthritis, 0 104 per cent, 0 100 per cent Case, M C, chronic polyarthritis, 0 103 per cent, 0 109 per cent

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28 Geyelin, H R The Archives Int Med, 1915, **16,** 975

29 Unpublished experiments

30 Cushing, H The Pituitary Body and Its Disorders, Philadelphia J B Lippincott Company, 1910, p 130

31 Porges, O Ztschr f klin Med, 1909-1910, **69,** 341, Janney Unreported observation

Experimental Demonstration of Hypoglycemia After Removal of Ductless Glands—If the metabolic picture which we found in muscular dystrophy is really the result of dysfunction of the endocrine organs, it should be possible to reproduce it essentially through removal of one or more ductless glands in animal experiments In the case of the epinephric bodies some data is available, as hypoglycemia has been reported after epinephrectomy [32] These experiments are subject, however, to some question, as death ensues under these circumstances, and the decrease in the blood sugar has been explained as an immediate antemortem phenomenon [33]

Recent experiments by Janney and Isaacson[34] are not open to this objection and seem conclusive as far as the thyroid may be concerned The blood glucose, blood and urinary sugar tolerance, also creatinin creatin metabolism were studied in a series of dogs before and after thyroidectomy As a result, a marked hypoglycemia, delayed blood sugar curve and other metabolic changes were observed These experiments will be reported in detail and will not therefore be reviewed here Suffice it to say that the changes described were quite definite and seem to represent the first clear cut demonstration that the abolition of the function of an endocrine organ leads to hypoglycemia Indeed, the knowledge gained by this work has been applied in the present clinical study

CHEMOPATHOLOGIC CONSIDERATIONS

The so-called pseudohypertrophy of certain muscle groups is characteristic of this disease Fulda's[35] view that the muscle enlargements are physiologic hypertrophy is not justified by the limited material presented by him A real hypertrophy is an increase in the number of normal muscle fibers and the bulk of sarcoplasm present in the muscle The findings in muscular dystrophy are not these Thus Morpurgo[36] observed that normal hypertrophied muscle did not show the splitting and loss of angular contour of the fibers, proliferation of connective tissue and fat deposition exhibited by specimens from muscular dystrophy cases Spiller[37] in his pathologic studies thought that the many nuclei present in dystrophic muscle possibly indicative of growth He, however, very properly emphasized that the other histologic anomalies were the same changes originally described by Erb, hence degenerative

32 Bierry, H, and Malloizel, L Compt rend Soc de biol, 1908, **65,** 232
33 Frank, E, and Isaac, S Ztschr f exper Path u Therap, 1909, **7,** 326
34 Janney, N W, and Isaacson, V I Proc Soc Exper Biol and Med, 1917, **14,** 99
35 Fulda, F Deutsch Arch f klin Med, 1894-1895, **54,** 525
36 Morpurgo, B Virchows Arch f path Anat, 1897, **150,** 522
37 Spiller, W G Med Rec New York, 1898, **54,** 9

in character Darkschewitsch[38] says that in the various types of muscular atrophies it is not uncommon to find besides the atrophic fibers, others of a size far in excess of normal muscle Hence the nuclear proliferation observed by Spiller in muscular dystrophy may, in our opinion, represent an imperfect effort toward compensation for the great number of fibers already atrophied

The experimental data presented in this article and the foregoing discussion emphasize the important part played by the disturbance of carbohydrate metabolism in the pathology of muscular dystrophy There remains to consider whether this new data will aid us in interpreting the histologic phenomena peculiar to the disease It is known how important carbohydrate pabulum is to muscle work and repair The blood of muscular dystrophy patients, as we have seen, supplies a greatly diminished amount of carbohydrate to the muscles The effect can readily be supposed to be a tendency to extensive degeneration of muscular tissue This might account for the histologic picture The lipomatosis of the dystrophic muscle groups is not a result of normal catabolism, but is a metabolic phenomenon distinctive of this muscle disease The defective carbohydrate metabolism may very possibly have a causal connection with these fat deposits, for it is known that other organs such as the liver are apt to become the special seat of fatty depositions when their carbohydrate metabolism becomes abnormal It is a striking fact that the dystrophic pseudohypertrophy is usually limited to certain muscle groups, calves, thighs and deltoids, which are used very constantly In explanation, it may be suggested that the profoundest metabolic disturbances may take place in such muscle groups because their constant activity may render the repair processes, already inhibited on account of hypoglycemia, inadequate As a result the degenerative changes already described may occur This hypothesis seems attractive

In our series several cases showed unusual depositions of fat in the mammary and inguinal regions The case of Levi and de Rothschild,[39] quoted by Délille,[40] exhibited at the seventh year an asthenic myopathy associated with lipomatosis and other symptoms indicative of endocrine disease Such abnormalities in the distribution of fat are present in other diseases as hypopituitarism, likewise characterized by disturbances in the carbohydrate metabolism Thus it will be remembered that 50 per cent of diabetics give a history of previous adiposity

38 Handbuch der Pathologischen Anatomie des Nervensystems, Berlin, 1904, **1,** 1259, chapter on "Hypertrophie der Muskeln"

39 Levi, L, and de Rothschild, H Rev d'hyg et de med inf, 1907, **6,** 309

40 Delille, A L'hypophyse et la Medication Hypophysaire, Paris, 1909

QUESTION AS TO WHAT ENDOCRINE GLANDS ARE INVOLVED IN MUSCULAR DYSTROPHY

Opinions as to the nature of the endocrine disfunction are divergent Indeed, even the pertinent inquiry has been raised by Parhon and Savini[41] as to whether the various atrophic ductless glands observed in dystrophy cases are primary or secondary Following this line of reasoning these authors devised an ingenious hypothesis that the myopathic changes of the disease under discussion might be favorably influenced by building material already present in the muscle Two children were accordingly fed with an extract of fetal muscle Improvement is said to have followed this treatment

Most authors, however, incline to consider a primary endocrine disturbance Various attempts have been made to elucidate its exact nature Thus, Markeloff[42] at Petrograd injected various glandular substances into dogs and measured the muscular activity with the ergograph or kymograph on electric stimulation The thyroid, hypophysis, suprarenals and testicles were found to stimulate muscular functional activity, the remaining endocrine glands being inhibitory As regards the special gland involved, there is little accord Pende[43] holds that the thymus is involved, suggesting thymic asthma as a cause of the dyspneic attacks in muscular dystrophy, calling attention to the splenic hyperplasia and transformation of the bone marrow Such dyspneic attacks may well be due, however, to the exhaustion of the respiratory muscular mechanism

The theory of Chvostek[44] and of Lundborg[45] that the hypersecretion and hyposecretion of the parathyroids stands in causative relation to myasthenia gravis and tetany, respectively, finds strong opponents in Haberfeld[46] and other observers The effect of opotherapy in the asthenias has been discussed by Carnot [47] Claude[48] describes an instructive case of myopathy associated with anomalies described by this author as pluriglandular insufficiency and tentatively seeks the cause of muscular dystrophy in abnormal activity of the hypophysis and pineal glands Gautier[49] in making observations on thyroid therapy quotes

41 Parhon, C J, and Savini, E Rev Neurol, 1914-1915, **22,** 1215

42 Markeloff, G J Russk Vrach, 1913, **12,** 1291 For German version see Zentralbl f d ges Chir u i Grenzgeb, 1913-1914, **3,** 545

43 Pende, N Endocrinologia, Milan, 1916, p 996

44 Chvostek, F Wien klin Wchnschr, 1908, **21,** 37

45 Lundborg, H Deutsch Ztschr f Nervenh, 1904, **27,** 217

46 Haberfeld, W Virchows Arch f Path Anat, 1911, **203,** 282

47 Carnot, P Opotherapie, Monograph Paris, 1911

48 Claude, H Rev neurol, 1911, **21,** 257

49 Gautier, G L'opotherapie thyroidemie, monograph, Paris, 1913

Lepine's[50] and Egger's[51] favorable results in cases of primary myopathy Levi and de Rothschild, again, publish their favorable results on primary myopathies with hypophysis gland preparations McCrudden and Sargent's patient improved on epinephrin and pituitrin

In our own series roentgenographic studies were made with a view of determining a possible pineal involvement In two cases only were distinct shadows found in locations ascribed to the pineal That these shadows represent actual pathologic conditions in the pineal body is open to serious question Timme[52] in an interesting paper reports a probable pineal involvement in four cases from the same family This author calls attention to the muscular weakness observed in pineal disease and emphasizes the possible pineal origin of certain cases of muscular dystrophy

The thyroid gland seems in some instances to bear a relation to muscular dystrophy The similarity of the osseous changes in muscular dystrophy and thyroid disease has been alluded to previously Boveri[53] has reported several muscular dystrophy cases in which exophthalmic goiter was also present Von Werdt's[54] case of muscular dystrophy was found to have at postmortem a colloid struma of the thyroid and changes in other ductless glands Prager's[55] case was evidently one of muscular dystrophy in a hyperthyroid subject

In our own series the one positive clue as to the involvement of a special endocrine gland was presented by Case 9 In this case there was a definite combination of acromegaly with the typical pseudohypertrophic lesions of muscular dystrophy This case is strong evidence in favor of a causative connection between dyspituitarism and muscular dystrophy Bregman[56] also mentions among his several cases a boy of 19 years affected with the so-called heredity type of dystrophy whose hands and feet presented a disproportionate development of the bony framework which did not fit in with the otherwise very delicate configuration of the body Similar observations were made by Eulenberg[57] and were referred by him to atrophic changes in the bone system in analogy with the muscular changes

Awkward as this is from the standpoint of therapy, we must face the possibility of muscular dystrophy and perhaps other so-called primary myopathies being in reality merely symptom complexes caused

50 Lepine, R Lyon méd, 1896, **82,** 35
51 Egger, F Arch f Psychiat, 1896-1897, **29,** 400
52 Timme, W The Archives Int Med, 1917, **19,** 79
53 Boveri, P Semaine med, 1910, **30,** 145
54 Von Werdt, F Frankfort Ztschr f Pathol, 1908-1909, **2,** 577
55 Prager, M Dissertation (Erlangen) Furth, A Schroeder, 1891
56 Bregman, L E Deutsch Ztschr f Nervenh, 1898-1899, **14,** 254
57 Eulenburg, A Deutsch Med Wchnschr, 1896, **22,** 458

by deficient function, not of one but of various endocrine organs separately or coincidently affected This view seems reasonable when one considers that the symptoms which are known to represent dysfunction of one endocrine gland are often very similar or identical with the manifestations of the affection of another ductless gland Thus, stoppage of growth, adiposity and defective bone formation are known to result from lesions of either pituitary, thyroid or sex glands If then, these symptoms are connected with such widely different organs, it seems not improbable that muscular dystrophy may likewise prove to represent a symptom complex capable of being caused by dysfunction of various ductless glands singly or together Therefore, we do not ascribe muscular dystrophy to hypothyroidism, as might seem justified from our experiments already alluded to The fact that the hypophysis was unquestionably affected in one case and the pineal possibly in two others, illustrates how difficult it would be to explain our series of cases on a hypothyroid or hypophysis basis Finally, it is hoped that the present research may, in helping to establish the endocrine origin of muscular dystrophy, serve to stimulate therapeutic efforts as well as metabolic investigations of the so-called primary myopathies

STUDIES IN ACUTE NEPHRITIS*

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In this communication I wish to present certain observations recently made on three cases of acute nephritis that were admitted to the medical wards of the Royal Victoria Hospital The patients were admitted at the onset of the condition and were studied until convalescence was well established Two of the cases have been subsequently followed for a prolonged period Observations were made as nearly simultaneously as possible by four methods which I believe give the most valuable data obtainable in kidney function studies These four methods are (1) the test meal, (2) the estimation of the rate of excretion of urea, (3) the determination of the calculated and actual blood plasma chlorids in coordination with their rate of excretion, and (4) the phenolsulphonephthalein test

The Nephritic Test Meal —The nephritic, or better the kidney function, test meal, as first advanced by Hedinger and Schlayer,[1] and later elaborated by Mosenthal[2] and O'Hare,[3] has proved to be of great value in estimating the ability of the kidney to eliminate fluid, salt and nitrogen After a study of some 200 meals, given in this clinic according to the Mosenthal technic, I think that the total balances of fluid, salt and nitrogen are of little value, as in most cases the intake is accurately known only during the twenty-four hours of the test The three points which I consider to be of the most importance are (*a*) the volume of the night urine, (*b*) the variation of specific gravity throughout the twenty-four hours, and (*c*) the concentration of nitrogen at night Even the last point, the ability of the kidneys to concentrate nitrogen at night, must be considered conservatively, since Mosenthal[4] recently has shown that there are certain kidneys, apparently normal in all other respects, that fail in this function

Excretion of Urea and of Chlorids—The rates of excretion of urea and of chlorids have been studied according to McLean's[5] method For the former, we have derived both his index and the Ambard con-

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* I should like to express my appreciation of a grant from the James Cooper Fund of McGill University which made this work possible

1 Hedinger and Schlayer Deutsch Arch f klin Med, 1914, **114**, 120

2 Mosenthal The Archives Int Med, 1915, **16**, 733

3 O'Hare The Archives Int Med, 1916, **17**, 711

4 Personal Communication

5 McLean Jour Exper Med, 1915, **22**, 212

stant, for the latter, the calculated and actual blood plasma chlorids, as well as the chlorid threshold

The Phenolsulphonephthalein Test—The phenolsulphonephthalein test has been performed according to Rowntree and Geraghty's[6] original technic, 0 006 gm of the dye being injected intramuscularly into the lumbar region and ten minutes allowed for the dye to reach the kidneys One and two hour specimens were collected

The methods used are for

Total Nitrogen Kjeldahl-Gunning modification

Urea Van Slyke and Cullen's[7] modification of Marshall's urease method

Ammonia Folin's[8] micromethod

Chlorids (in both blood plasma and urine) McLean and Van Slyke's[9] method

Blood Sugar Lewis and Benedict's[10] original technic

REPORT OF CASES

A brief synopsis of the three cases follows, and the laboratory notes are given in full

CASE 1 (Medical No 24738) *History*—A man, aged 55, was admitted to the Royal Victoria Hospital, Oct 24, 1916, complaining of swelling of feet and legs, shortness of breath, and headache

The patient was in usual health until four days previously, when he noticed swelling and soreness of the left ankle The next day his right ankle also became sore and swollen, which was followed by a generalized edema of both legs At this time he began to suffer from headaches and shortness of breath on exertion Two days later the headaches became much worse His personal history was negative except that he had scarlet fever when a child, and there was nothing of importance in his family history

Examination—He was a well developed, middle aged man, the muscles were of good tone, but he was unable to lie on the left side without coughing and becoming dyspneic The digestive, genito-urinary, locomotor and integumentary, lymphatic and nervous systems were normal, also the fundi were normal

Respiratory System At the right base behind there was a triangular area of dulness extending upward to the level of the seventh dorsal spine and laterally to the anterior axillary line Over this area the percussion note was flat, tactile fremitus was absent, and breath and voice sounds were much diminished

Cardi of Circulatory System The pulse was regular but tension was increased The cardiac transverse dulness was 14 cm at the level of the fourth space, otherwise negative

Temperature and Pulse On admission there was a slight evening temperature of 100 F, which dropped very gradually, reaching the normal on November 27 While the evening temperature was present the pulse rate averaged from 90 to 100, dropping to a level of from 70 to 80 as the temperature fell

6 Rowntree and Geraghty THE ARCHIVES INT MED, 1912, **9,** 284
7 Van Slyke and Cullen Jour Biol Chem, 1914, **19,** 211
8 Folin and MacCallum Jour Biol Chem, 1912, **11,** 523
9 McLean and Van Slyke Jour Biol Chem, 1915 **21,** 361
10 Lewis and Benedict Jour Biol Chem, 1915, **22,** 61

TABLE 1—A RECORD OF THE OBSERVATIONS MADE ON THE RATE OF—
Case 1 Medical No 24738—

Date	Weight, Kg	Urine, per 24 Hours, C c	Urea				
			Gm per Liter of Blood, Ur	Gm per Liter of Urine, C	Gm per 24 Hours D	McLean's Index	Ambard Constant
10/28/16							
11/ 6/16	69 8	2,160	0 858	14 16	20 57	17 0	0 194
11/14/16	66 4	3,456	0 870	10 00	34 56	19 6	0 181
11/20/16	65 9	3,000	0 852	7 16	21 48	10 8	0 243
12/ 1/16	63 2	3,888	0 780	2 97	11 55	4 6	0 371
12/ 8/16	62 0	4,992	0 810	2 07	10 33	3 2	0 442
12/14/16	61 1	3,744	0 810	2 97	11 11	4 3	0 391
12/28/16	60 3	2,880	1 530	9 19	28 51	5 2	0 329
1/ 2/17	60 9	3,768	1 140	4 96	18 43	4 8	0 370
1/10/17	59 5	4,176	0 600	2 94	12 26	8 9	0 269
1/13/17	60 4	5,112	0 570	1 65	8 43	4 6	0 370
1/25/17	60 2	4,872	0 420	2 37	11 54	15 0	0 212
2/ 2/17	63 9	3,792	0 390	5 37	20 35	43 5	0 110
2/ 9/17	63 9	4,104	0 570	4 74	19 45	18 4	0 188
2/16/17	64 1	3,792	0 480	4 08	15 46	19 0	0 185
2/23/17	65 7	5,472	0 540	4 65	25 44	25 7	0 159
3/ 9/17	66 4	5,592	0 660	4 65	25 99	17 4	0 192
3/24/17	66 7	1,800	0 630	14 34	25 81	33 1	0 139
4/ 6/17	76 5	2,568	0 510	10 06	25 82	42 0	0 124
4/20/17	68 3	4,320	0 585	6 66	28 77	28 5	0 149
5/ 4/17	68 4	3,696	0 510	7 74	28 56	40 0	0 126
5/18/17	68 5	5,328	0 630	4 11	21 89	14 7	0 210
6/ 1/17	69 2	2,040	0 585	14 04	28 64	40 5	0 126
6/22/17	67 5	5,000	0 585	5 29	26 45	23 5	0 165
7/ 6/17	68 1	3,552	0 540	3 99	14 16	12 7	0 226

—UREA AND CHLORID EXCRETION AND ON PHENOLSULPHONEPHTHALEIN TEST
—Diagnosis Acute Nephritis

Sodium Chlorid					Thresh-old	Phenol-sulphone-phthalein, Two Hours, per Cent	Remarks
Gm per Liter of Urine, C	Gm per 24 Hours, D	Gm per Liter of Plasma					
		Calculated	Actual	Difference			
						86	Edema of lower limbs
2 61	5 64	5 695	6 556	+0 861	6 381		Albumin = 8 gm per liter
3 15	10 87	5 964	6 687	+0 723	6 343		
3 1	7 65	5 840	6 125	+0 285	5 905		
1 68	6 52	5 798	5 937	+0 139	5 759	Trace	Albumin, 2 gm per liter
2 43	12 13	5 888	5 937	+0 039	5 669	Trace	
1 4	5 23	5 775	5 687	—0 088	5 532	15	
2 6	7 48	5 837	6 25	+0 413	6 033	20	
2 4	9 04	5 853	6 50	+0 647	6 267		No red blood cells
1 0	4 17	5 748	5 47	—0 278	5 342	24	Jan 9, 1917, theophyllin, 15 grains
0 62	3 16	5 718	6 062	+0 344	5 964		Albumin, a trace
1 62	7 87	5 819	6 062	+0 243	5 863	41	Discharged Jan 27, 1917
6 94	26 30	6 126	7 062	+0 936	6 556	42	Ate extra salt
6 0	24 62	6 092	7 062	+0 97	6 59	40	
3 25	12 31	5 906	6 750	+0 844	6 464		Albumin = 0
3 37	18 43	5 969	6 625	+0 656	6 276	40	
3 4	19 01	5 973	6 437	+0 464	6 084	46	
8 7	15 66	6 024	6 625	+0 601	6 221	41	
6 2	15 92	5 992	6 625	+0 633	6 253	34	
5 6	24 19	6 065	6 312	+0 247	5 867	51	Albumin = 0
5 7	21 06	6 037	6 312	+0 275	5 895	41	
2 4	12 78	5 881	6 000	+0 119	5 739		Albumin, a trace
7 7	15 70	6 006	6 062	+0 056	5 676	51	
2 6	13 0	5 89	5 937	+0 047	5 667	57	Albumin = 0
1 6	5 68	5 778	5 625	—0 153	5 467	56	

Blood Pressure Oct 24, 1916, the systolic pressure was 150, and the diastolic 115 mm of mercury These gradually dropped, the most prompt reduction taking place in the diastolic pressure

BLOOD PRESSURE

Date	Systolic	Diastolic
Nov 20, 1916	140	100
Jan 4, 1917	140	90
Jan 10, 1917	135	90
Jan 15, 1917	130	95
Jan 25, 1917	130	90
Feb 3, 1917	150	110
March 9, 1917	144	92
April 20, 1917	140	90
May 4, 1917	124	90
June 1, 1917	126	80

Blood Oct 26, 1916, the red blood cell count was 4,200,000, white blood cell count, 9,400, and the hemoglobin 50 per cent (Sahli)

Urine Oct 24, 1916 The urine was of an amber color with a "smoky" appearance, acid in reaction, with a specific gravity of 1,021 There were 8 gm per liter of serum albumin and the microscopic examination showed large numbers of red blood cells, granular and cellular casts

Oct 28, 1916, 1,650 c c of opalescent, yellowish fluid were withdrawn from the right pleural cavity The specific gravity was 1 012 and it contained 200 cells per cubic millimeter, mostly small mononuclears

The results of the study of the kidney function are shown in the accompanying tables Table 1 gives the observations made on the rate of urea and chlorid excretion as well as on the phenolsulphonephthalein test The diet throughout the period of these observations is shown in Table 2, the dates indicating a change

TABLE 2—THE DIET GIVEN THROUGHOUT THE PERIOD OF OBSERVATIONS RECORDED IN TABLE 1

Date	Diet	Sodium Chlorid	Fluid Total, C c
10/31/16	Restricted protein		1,000
11/11/16	Low protein diet ,	Salt free	1,000
12/ 8/16	Low protein diet	Salt free	2,000
12/12/16	Protein, 52, fat, 60, carbohydrate, 100	Salt free	2,000
12/17/16	Protein, 60, fat, 65, carbohydrate, 150	Salt free	2,000
12/29/17	Low protein diet	Salt free	2,000
1/26/17	Protein, 52, fat, 60, carbohydrate, 100	Salt-free	2,000
1/27/17 discharged	Restricted protein	Restricted salt in cooking, no free salt	

Three nephritic test meals that show the changes in function in relation to the rate of excretion of urea and chlorids are given in full The first was administered during the period of acute inflammation, the second during that of greatly impaired function, and the third at the time of convalescence

TABLE 3—RESULTS OBSERVED AFTER THE ADMINISTRATION OF NEPHRITIC TEST MEALS

Case 1 Nov 15, 1916 Meal given during the period of acute inflammation

Time of Day	Urine, C c	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent	Gm	Per Cent	Gm
8–10	122	1 015				
10–12	170	1 014				
12– 2	165	1 015				
2– 4	160	1 014				
4– 6	170	1 015				
6– 8	140	1 015				
Total day	927		0 290	2 67	0 574	5 30
Night, 8-8	960	1 013	0 418	4 03	0 539	5 18
Total 24 hours	1,887			6 70		10 48
Intake	1,760			8 4		13 4
Balance	—127			+1 7		+2 92

Case 1 Jan 20, 1917 Meal given during period of greatly impaired function

Time of Day	Urine, C c	Specific Gravity	Sodium Chlorid Per Cent	Sodium Chlorid Gm	Nitrogen Per Cent	Nitrogen Gm
8–10	168	1 013				
10–12	118	1 016				
12– 2	33	1 019				
2– 4	79	1 020				
4– 6	121	1,016				
6– 8	106	1 018				
Total day	625		0 318	1 97	0 371	2 30
Night, 8-8	620	1 016	0 328	1 93	0 387	2 39
Total 24 hours	1,245			3 90		4 69
Intake	1,760			8 5		13 4
Balance	+515			+4 6		+8 71

Case 1 March 23, 1917 Meal given during convalescence

Time of Day	Urine, C c	Specific Gravity	Sodium Chlorid Per Cent	Sodium Chlorid Gm	Nitrogen Per Cent	Nitrogen Gm
8–10	103	1 022				
10–12	62	1 024				
12– 2	98	1 025				
2– 4	104	1 026				
4– 6	118	1 025				
6– 8	130	1 023				
Total day	615		0 77	4 69	0 97	5 91
Night, 8-8	517	1 024	0 66	3 36	1 02	5 20
Total 24 hours	1,132			8 05		11 11
Intake	1,760			8 5		13 4
Balance	+628			+0 45		+2 29

CASE 2 (Medical No 25374) *History*—A man, aged 30, was admitted to the Royal Victoria Hospital, March 6, 1917, complaining of "Cold in the chest" His present illness began ten days previously with a cold that was rapidly followed by a severe sore throat, hoarseness, and cough with expectoration With the onset of cough he had several slight chills followed by sweats For the previous week the urine had been of a dark brown color His personal and family history were unimportant

TABLE 4—RESULTS OF THE STUDIES MADE ON THE RATE OF UREA AND—

Case 2 Medical No 25374—

Date	Weight, Kg	Urine, per 24 Hours, C c	Urea: Gm per Liter of Blood, Ur	Urea: Gm per Liter of Urine, C	Urea: Gm per 24 Hours D	Urea: McLean's Index	Urea: Ambard Constant
3/ 9/17	76 0	1,104	0 540	10 78	11 88	15 8	0 203
3/15/17	75 4	1,584	0 570	17 38	27 52	42 0	0 124
3/28/17	71 4	936	0 555	23 4	21 84	43 0	0 122
4/ 4/17	71 7	1,056	0 360	18 79	19 82	83 0	0 088
4/10/17	70 4	1,632	0 435	17 44	28 44	80 0	0 089
4/17/17	71 7	1,920	0 345	12 28	23 57	87 0	0 086
4/24/17	71 7	4,368	0 352	7 68	33 53	94 0	0 083
5/ 1/17	71 3	2,712	0 285	10 0	27 12	133 0	0 069
5/ 8/17	72 3	864	0 270	16 2	13 99	95 0	0 082
5/16/17	72 6	1,464	0 255	13 63	19 15	135 0	0 069

Examination He was a well developed and nourished young man The physical examination was negative except for an inflamed throat and diffuse, large, moist râles over both sides of the chest The fundi were normal

On admission the temperature was 101 F, but it rapidly dropped to an evening temperature of 99 F, which was maintained until March 23

Blood Pressure Systolic, 130, diastolic, 70 Further estimations failed to show any variations

Urine March 7, 1917, this was observed to be brown and "smoky" with a specific gravity of 1 015, there were 4 gm of albumin per liter, with red blood cells, cellular and granular casts

Table 4 gives the results on the rate of urea and chlorid secretion and the phenolsulphonephthalein test

CASE 3 (Medical No 24890) *History*—A boy, aged 15, was admitted to the Royal Victoria Hospital Dec 3, 1916 The patient complained of swelling of face and ankles and difficulty in passing urine He was in usual health until twelve days previously, when he caught cold At the onset he had chilly sensations and his face and ankles became swollen He had no polyuria, but during the previous week micturition had been painful The patient had scarlet fever, with a normal convalescence, when 5 years of age The family history was unimportant

Examination The patient was a fairly well nourished boy, the mucous membranes were pale and around both eyes and ankles there was marked edema The examination was otherwise negative The temperature was normal, also the fundi

Blood Pressure

Date	Systolic	Diastolic
Dec 4, 1916	130	80
March 2, 1917	140	88
April 20, 1917	120	60
May 4, 1917	128	88

—of Chlorid Excretion and the Phenolsulphonephthalein Test
—Diagnosis Acute Nephritis

Sodium Chlorid					Threshold	Phenol sulphone phthalein, Two Hours, per Cent	Remarks
Gm per Liter of Urine, C	Gm per 24 Hours, D	Gm per Liter of Plasma					
		Calculated	Actual	Difference			
2 5	2 76	5 736	6 125	+0 389	6 009	59	Slight edema of legs, albumin = 4 gm per liter
4 56	7 20	5 84	6 562	+0 722	6 342	79	
3 5	3 27	5 763	6 50	+0 737	6 357	72	
3 87	4 08	5 783	5 875	+0 092	5 712	73	Albumin = 2 gm per liter
3 37	5 49	5 804	5 843	+0 039	5 659	74	
4 81	9 23	5 879	5 906	+0 027	5 647	75	Albumin, a trace
4 12	17 97	5 966	6 200	+0 234	5 966		
5 68	15 40	5 968	5 812	—0 156	5 464	48	
7 18	6 19	5 853	5 937	+0 084	5 704	81	
9 93	14 53	6 006	6 062	+0 056	5 676	85	Discharged Albumin a trace

TABLE 5—The Diet Prescribed in Case 2 During the Study of the Kidney Excretions

Date	Diet	Sodium Chlorid	Fluid Intake, C c
3/ 6/17	Restricted protein	Salt-free	1,500
3/14/17	Protein, 52, fat, 73, carbohydrate, 118	Salt free	1,500
3/20/17	Protein, 64, fat, 86, carbohydrate, 187	Salt free	1,500
4/11/17	Protein, 80, fat, 90, carbohydrate, 250	Salt free	1,500

Two nephritic test meals, one shortly after admission and one late in convalescence, are given in full The second shows a marked impairment of function

Blood Dec 5, 1916, the red blood cell count was 3,305,000, white blood cells, 7,000, and the hemoglobin was 55 per cent (Sahli)

Urine Dec 4, 1916, the color was reddish amber, specific gravity 1,020, with 6 gm of albumin per liter Microscopically there were many red blood cells, granular and cellular casts

Table 8 gives in full the urea and chlorid studies and the phenolsulphonephthalein tests

TABLE 6—Record of Results Following Nephritic Test Meals

Case 2 March 8, 1917 Administered shortly after admission

Time of Day	Urine, C c	Specific Gravity	Sodium Chlorid Per Cent	Sodium Chlorid Gm	Nitrogen Per Cent	Nitrogen Gm
8-10	135	1 018				
10-12	155	1 017				
12- 2	190	1 016				
2- 4	135	1 015				
4- 6	168	1 016				
6- 8	185	1 015				
Total day	968		0 26	2 52	0 886	8 50
Night, 8-8	720	1 018	0 22	1 58	0 992	7 04
Total 24 hours	1,688			4 10		15 54
Intake	1,760			7 5		13 4
Balance	+72			+3 4		—2 14

Case 2 May 14, 1917 Administered late in convalescence

Time of Day	Urine, C c	Specific Gravity	Sodium Chlorid Per Cent	Sodium Chlorid Gm	Nitrogen Per Cent	Nitrogen Gm
8-10	111	1 026				
10-12	112	1 023				
12- 2	145	1 018				
2- 4	171	1 016				
4- 6	116	1 020				
6- 8	118	1 023				
Total day	773		0 72	5 58	0 63	4 90
Night, 8-8	740	1 018	0 62	4 62	0 62	4 59
Total 24 hours	1,513			10 20		9 49
Intake	1,760			8 5		13 4
Balance	+247			—1 70		+3 91

DISCUSSION OF RESULTS

The first two cases may be grouped together, as they both show an involvement of the kidney's ability to eliminate nitrogen and chlorids, while the third may be considered to be a true chlorid case

Case 1 Impairment in Rate of Urea Excretion with Convalescence — In this case the main point that I wish to emphasize is the marked impairment in the rate of urea and of phenolsulphonephthalein excretion starting on December 1 Simultaneously the actual concentration of blood plasma chlorid and the level of the chlorid threshold show a return to practically normal figures This prolonged extreme impairment in the rate of urea excretion first appeared at the time when the patient started to show marked improvement in the general clinical condition From December 1 to January 13, clinically, he improved rapidly, his anemia disappeared, strength returned and hematuria rapidly subsided The hematuria had completely disappeared by January 2, and the albuminuria, 8 gm per liter at the onset, had dropped to a slight trace At no time was there any serum globulin in the urine

Case 2 —Steady Improvement in Function —In contrast to the findings in Case 1 are those of Case 2, in which there was no slump in function, the rate of urea and of phthalein excretion improving from the onset The general clinical condition of the patient ran parallel to the functional findings On considering this point I believe that the marked and prolonged slump in function, as shown in Case 1, was due to a subsidence of the acute inflammatory condition present in the kidneys at the onset Evidently, if an acute nephritis is severe enough, the function is hyperactive As the inflammation subsides and the stimulation is removed the kidneys display a function which is more truly an index of the actual state of affairs This is the critical period in any case of acute nephritis, as it is during this prolonged rest that great care must be taken not to overstrain the exhausted function That this low level of function is often of much longer duration than supposed might be indicated by the results in Case 1

In contrast to Case 1 are the findings in Case 2, in which there is no slump, but a steady improvement in function This is explained, I believe, by the fact that the original inflammation was not severe enough to cause a hyperactive organ, rather the rate of urea excretion was in proportion to the disturbed process, and accordingly became a true index of the severity of the condition Such would be the findings in the milder types of acute nephritis Nevertheless, the function, as shown by the second test meal, has not improved to such an extent as the results in the rate of excretion of urea and of chlorids would indicate

TABLE 7—Record in Detail of the Studies Respecting Urea—Case 3 Medical No 24800—

Date	Weight, Kg	Urine, per 24 Hours, C c	Urea				
			Gm per Liter of Blood, Ur	Gm per Liter of Urine, C	Gm per 24 Hours D	McLean's Index	Ambard Constant
12/ 4/16	50 0	4,800	0 42	12 67	60 81	220	0 054
12/ 8/16	47 7	2,722	0 27	5 4	14 64	88	0 065
12/20/16	40 8	3,936	0 46	7 87	30 96	98	0 081
1/ 2/17	40 9	1,440	0 45	18 51	26 64	124	0 072
1/13/17	40 7	1,056	0 39	18 12	18 91	117	0 074
1/26/17	41 1	10,968	0 18	0 51	5 59	27	0 157
2/ 2/17	40 7	1,680	0 36	15 63	26 25	177	0 060
2/ 9/17	40 6	1,368	0 30	17 82	24 37	252	0 055
2/16/17	40 8	370	0 27	25 65	9 48	144	0 069
3/ 2/17	43 2	2,496	0 135	6 09	15 19	427	0 039
3/16/17	45 4	5,760	0 12	2 23	12 84	264	0 049
4/ 6/17	47 1	1,320	0 255	18 01	23 76	295	0 047
4/20/17	47 5	1,296	0 255	13 02	16 93	178	0 060
5/ 4/17	47 4	1,848	0 315	20 32	37 53	324	0 044
5/18/17	48 2	5,424	0 265	5 04	32 13	192	0 058
6/ 1/17	47 6	2,160	0 285	12 85	27 75	231	0 053
6/22/17	50 1	972	0 28	22 75	22 10	238	0 052
7/ 6/17	46 9	4,080					

—AND CHLORID EXCRETION AND THE PHENOLSULPHONEPHTHALEIN TESTS
—Diagnosis Acute Nephritis

Sodium Chlorid					Threshold	Phenol sulphone phthalein, Two Hours, per Cent	Remarks
Gm per Liter of Urine, C	Gm per 24 Hours, D	Gm per Liter of Plasma					
		Calculated	Actual	Difference			
6 12	29 37	6 205	6 875	+0 67	6 29	36	Edematous
5 56	15 07	6 04	6 937	+0 897	6 517		Albumin = 6 gm per liter
1 68	6 6	5 842	7 162	+1 320	6 940	81	
3 56	5 11	5 856	6 900	+1 044	6 664	81	
2 87	3 02	5 792	6 625	+0 833	6 453		Jan 25, 1917, theophyllin, 15 grains
0 62	6 84	5 796	6 718	+0 922	6 542		Albumin = 2 gm per liter
6 45	10 82	6 02	6 875	+0 855	6 475		
7 18	9 82	6 011	6 750	+0 739	6 359		Albumin = 0 5 gm per liter
4 87	1 79	5 771	6 687	+0 916	6 536	85	Feb 22, 1917, discharged
4 43	11 04	5 977	6 562	+0 585	6 205	74	
2 06	11 86	5 890	7 037	+1 147	6 767	89	Ate extra salt
6 62	9 73	5 974	6 625	+0 651	6 271	82	Albumin, heavy trace
7 13	9 24	5 970	5 969	—0 001	5 619	55	
2 68	4 95	5 821	6 062	+0 241	5 861	80	
2 12	11 52	5 907	6 062	+0 155	5 775		
3 37	7 29	5 877	5 812	—0 065	5 555	84	
6 0	3 83	5 880	5 625	—0 255	5 365	83	Albumin, a trace
1 3	5 30	5 775	5 437	—0 338	5 262	86	

TABLE 8—Diet in Connection with the Observations Recorded in Table 7

Date	Diet	Sodium Chlorid	Fluid Intake, C c
12/10/16	Protein, 61, fat, 85, carbohydrate, 127	Salt-free	1,500
12/17/16	Protein, 82, fat, 91, carbohydrate, 139	Salt free	1,500
1/17/17	Low protein diet	Salt-free	1,500
1/27/17	Protein, 82, fat, 91, carbohydrate, 139	Salt free	1,500
2/13/17	Protein, 79, fat, 119, carbohydrate, 149	Salt free	1,800

The results of the study of one nephritic test meal carried out on admission is recorded in Table 9

TABLE 9—A Study of the Results Following a Nephritic Test Meal
Case 3 Dec 4, 1916

Time of Day	Urine, C c	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent	Gm	Per Cent	Gm
8-10, 10-12	192	1 019				
12- 2	120	1 019				
2- 4	105	1 020				
4- 6	129	1 020				
6- 8	140	1 019				
Total day	686		0 60	4 08	1 00	6 86
Night, 8-8	375	1 018	0 58	2 14	0 85	3 14
Total 24 hours	1,061			6 22		10 00
Intake	1,680			8 2		9 4
Balance	+619			+1 98		—0 6

Case 3 Functional Disturbances Confined to Excretion of Chlorids — The third case is one in which the chlorid function is at fault and demonstrates rather well the possible duration of the disturbance even when on a salt-free diet, since it requires six months to bring the threshold to a normal level Throughout, the rate of urea excretion was not impaired The phenolsulphonephthalein, except for the first estimation on December 6, remained within normal limits

Edema—All three of the cases showed a moderate amount of edema on admission This condition was most marked in Case 3 The edema disappeared long before the chlorid threshold had reached normal levels, but did not reappear when at a later date their levels became temporarily raised Serum globulin failed to show in the urine in

Case 3, and the blood cholesterol remained normal, which would exclude it from the group of cases recently described by Epstein[11]

Relation of Nephritis to Glucose Threshold—The raised level of the glucose threshold present in many cases of acute nephritis is well shown in Case 1, in which, after 100 gm of glucose were administered by mouth on a fasting stomach, the following results were recorded, November 8

11 50 a m	0 100 per cent	No glucose
12 00 noon	100 gm glucose in black coffee	
1 00 p m	0 184 per cent	No glucose
2 00 p m	0 217 per cent	No glucose
3 00 p m	0 170 per cent	Faintest trace
4 00 p m	0 111 per cent	No glucose

On November 28 the test was repeated with the following results

7 45 a m	0 090 per cent	No glucose
8 00 a m	100 gm glucose in black coffee	
9 00 a m	0 152 per cent	No glucose
10 00 a m	0 156 per cent	No glucose
11 00 a m	0 122 per cent	No glucose
12 00 noon	0 120 per cent	No glucose
2 00 p m	0 080 per cent	No glucose

The foregoing results would indicate that the block for glucose was present only during the period of stimulation

Action of Theophyllin—There is another point which I wish to present In Case 1, 15 grains of theophyllin (theocin) were administered by mouth January 9, which was followed by a very marked diuresis lasting for two days Simultaneously with this diuresis the level of the chlorid threshold dropped to 5 342 gm per liter, January 10, returning to 5 964 gm per liter January 13 In Case 3, also, 15 grains of theophyllin were administered by mouth January 25, but there was no diuresis, and the chlorid threshold, January 26 was slightly raised to 6 542 gm per liter Simultaneously the McLean index fell from 117 to 27 This would indicate that in Case 3 the kidney failed to respond to the drug, accordingly showing an impairment of function rather than an improvement Following up these suggestions I have tried the action of theophyllin on normal and pathologic kidneys with results that seem to indicate that the drug acts on the chlorid threshold, allowing the chlorids to pass out of the blood stream, as well shown in Case 1 in which the blood plasma chlorid dropped from 6 50 to 5 47 gm per liter, the water following

In no case in which diuresis was not obtained was there a lowering of the chlorid threshold Usually when there was no diuresis the chlorid threshold became markedly raised and the rate of urea excretion impaired This is well shown in a chlorid case of chronic nephritis

11 Epstein Tr A M A, June, 1917

(Med No 25180) in which there was no diuresis, the chlorid threshold going from 6 114 to 6 640 gm per liter, with a drop in the rate of urea excretion from 212 to 69 (McLean's index) Further observations are being conducted on the action of theophyllin which will be reported at a subsequent date

SUMMARY

Studies have been conducted on three cases of acute nephritis which demonstrate the following points

1 In very severe cases of acute nephritis the kidney function during the early stages is much better than the actual state of the kidneys would seem to warrant This is due to the increased stimulation from which they are suffering

2 With the subsidence of the inflammation the function tends to fall to a very low level, which level is more truly an index of the kidney state As convalescence is established this level tends to return to that at which the kidneys remain permanently damaged This "slump" in function takes place simultaneously with a marked improvement in the clinical condition of the patient

3 Theophyllin probably acts in part by lowering the chlorid threshold, thereby allowing the chlorids to pass out of the blood plasma, water following

I should like to express my thanks to Miss Jacobson, my chemical technician, for her careful work in carrying out a large part of the chemical estimations

A PAPILLARY CARCINOMA OF THE KIDNEY WITH METASTASIS IN THE BRAIN *

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The relative infrequency of papillary carcinoma of the kidney proper reported in the literature is emphasized by Wohl[1] in his description of a malignant papillary adenoma of the kidney He says that his is the twelfth instance of such adenopapillary tumors appearing in the literature, but he probably has not included in this number a report by Eisenstaedt [2] The latter emphasizes the rarity of carcinoma of the renal parenchyma proper, and reports a tumor which in its microscopic characters resembles closely the one to be described It contained papillae having very little supporting tissue, each pierced centrally by a thin-walled vessel Kretschmer and Moody[3] in 1914 reviewed the reports of such tumors and found ten recorded They added another, making a total of eleven recorded at that time

At a necropsy performed by me for the purpose of establishing the cause of death, a soft fleshy tumor was found in the left kidney and a large tumor thrombus projected into the corresponding vein In addition, there was noted another tumor, definitely metastatic, in the anterior pole of the left temporal lobe of the brain The circumstances attending the illness of the deceased could not be obtained with any degree of certainty or detail

History—The patient was an adult 58 years and 6 months of age, a shipping clerk employed by a lumber company, who had been admitted to a hospital about eight weeks before his death with a history of having suffered a skull injury, the severity of which was not definitely known or determined At the time of his admission to the hospital he presented some disturbances in mentality, which, associated with the foregoing history of an injury, led the attending physician to diagnose a brain injury, and to trephine the calvarium About ten days after the first operation, a second exploration of the cranium was made and the original opening in the skull enlarged Two urine examinations made during the patient's stay in the hospital were reported as showing no blood or albumin The patient's condition was not improved by the surgical treatment and he gradually grew worse mentally, finally dying in a state of apathy and emaciation The presence of a tumor of the brain was not considered during the

* Submitted for publication Sept 6, 1917

* From the Department of Pathology, University of Chicago

1 Wohl, M G Malignant Papillary Adenoma of the Kidney, Surg, Gynec and Obst, 1917, **24,** 61

2 Eisenstaedt, J S Primary Adenocarcinoma of the Kidney, Urol and Cutan Rev, 1916, **20,** 61

3 Kretschmer, H L, and Moody, A M Malignant Papillary Cystadenoma of the Kidney with Metastases, Surg, Gynec and Obst, 1914, **19,** 766

clinical course of the disease The important anatomic findings noted during the necropsy concern chiefly the left kidney and the brain, there being no other metastases observed, except about a half dozen grayish-brown nodules, the largest 2 mm in diameter, scattered in the lung substance

Postmortem Examination—The left kidney was of about normal size (Fig 1) The renal vein was widely dilated by a tumor thrombus involving chiefly the two lowest branches of this vessel It projected bluntly into the lumen of the vein almost completely occluding it, and was 2 cm wide, 1 8 cm thick and 4 cm long In the posterior portion of the lower pole of the kidney proper was a very soft, fleshy tumor, irregularly outlined, about 4 cm by 4 5 cm in its maximum surface dimensions The kidney capsule over this area bulged slightly The tumor itself was gray, and so soft that only after hardening in 10 per cent formaldehyd solution was examination possible On the transversely sectioned surfaces of the posterior half of the bisected kidney the tumor tissue appeared as a continuous gray zone of a maximum width of 1 cm, lying between the cortex and medulla Its outline was irregular, but, in spite of its relatively small size, it had invaded extensively the venous blood system as the latter approached the pelvis of the kidney (Fig 2) In general the cortex of the kidney was involved to a greater extent than the medullary portion Careful examination of the renal pelvis and the ureter, as well as the left adrenal, disclosed no gross alterations of these structures

In the anterior pole of the left temporal lobe of the brain there was a reddish-brown area, irregularly round, 3 5 cm in its surface diameter, roughened, and not sharply demarcated from the surrounding brain tissue (Fig 3) The dura immediately covering this area was adherent, and had been invaded but not penetrated by tissue arising from the area mentioned There were no other striking changes on the outside of the brain except a slight opacity of the lepto opposite the site of the decompression operation Sections of the brain made after hardening demonstrated a rather extensive involvement of the anterior portion of the left temporal lobe The maximum vertical and transverse dimensions were 3 and 4 cm, and the same anteroposterior dimension was 4 cm The sectioned surfaces of the tumor were reddish-brown, consisting of gray areas of tumor tissue from 1 to 6 mm in width scattered with irregularly sized and located areas of necrosis and liquefaction Toward the posterior limits of the tumor and approaching the lateral ventricle on that side was a cyst 2 cm by 2 cm by 4 cm filled with a limpid brown fluid Its posterior limit was opposite approximately the same part of the basal ganglia, and lay immediately outside and above the lateral ventricle The tumor was clearly demarcated, but not encapsulated, merging without interruption into the surrounding brain tissue In consistency its tissue was very soft and friable There was some compression of the left lateral ventricle and displacement to the right of the brain tissue medial to the left lateral ventricle

Microscopic Examination—Histologic sections of the kidney showed a fairly constant structure (Fig 4) The tissue was cellular, with only a little supporting stroma The tumor cells were about the diameter of polymorphonuclear leukocytes, their nuclei being granular, indented, oval or round, occupying about two-thirds of the entire cell, the cytoplasm staining a light pink with eosin A rather striking feature microscopically was the radial arrangement of these cells about thin-walled, clearly defined capillaries, forming rosette-like structures about, or slightly larger than, the diameter of a normal kidney glomerulus, the center of such a structure being the cross section of a capillary Usually the width of a rosette was about ten to fifteen cells, although larger and smaller ones were also present From the periphery of the capillaries a delicate connective tissue stroma extended outward a short distance as narrow papillae covered by epithelium, the latter somewhat broken and disarranged by the manipulation and fixation of the tissues, but usually two to three cells in depth, the marginal portion of the rosette consisting chiefly of epithelial cells without

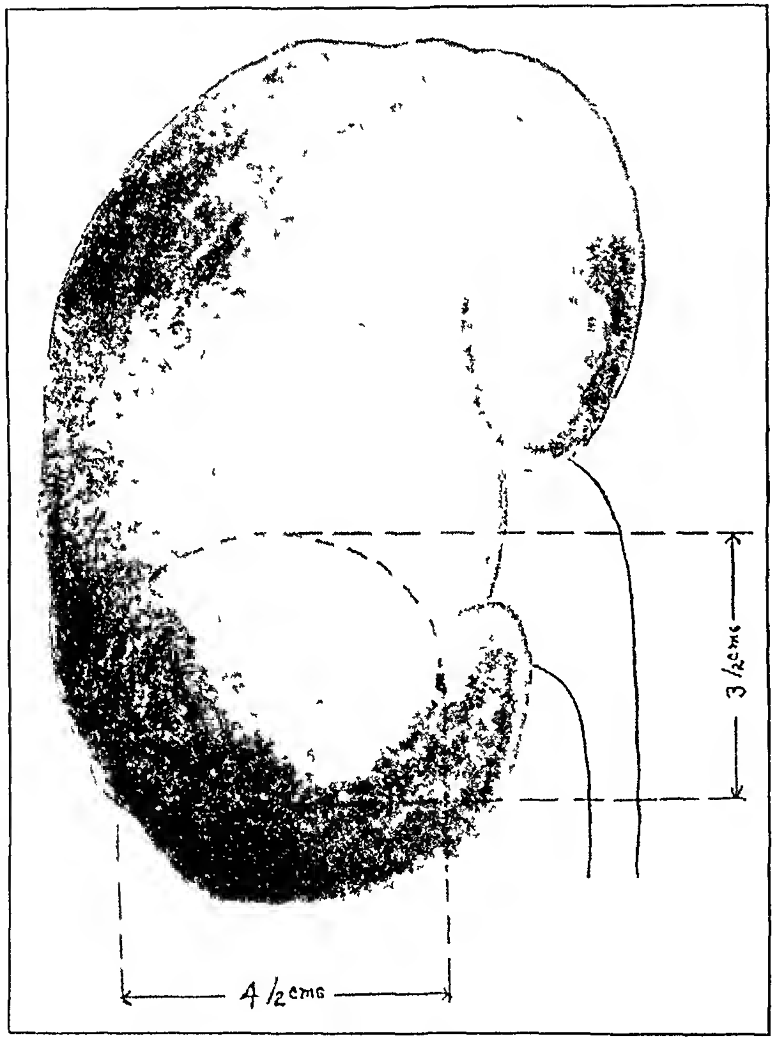

Fig 1—Drawing locating the primary tumor in the kidney

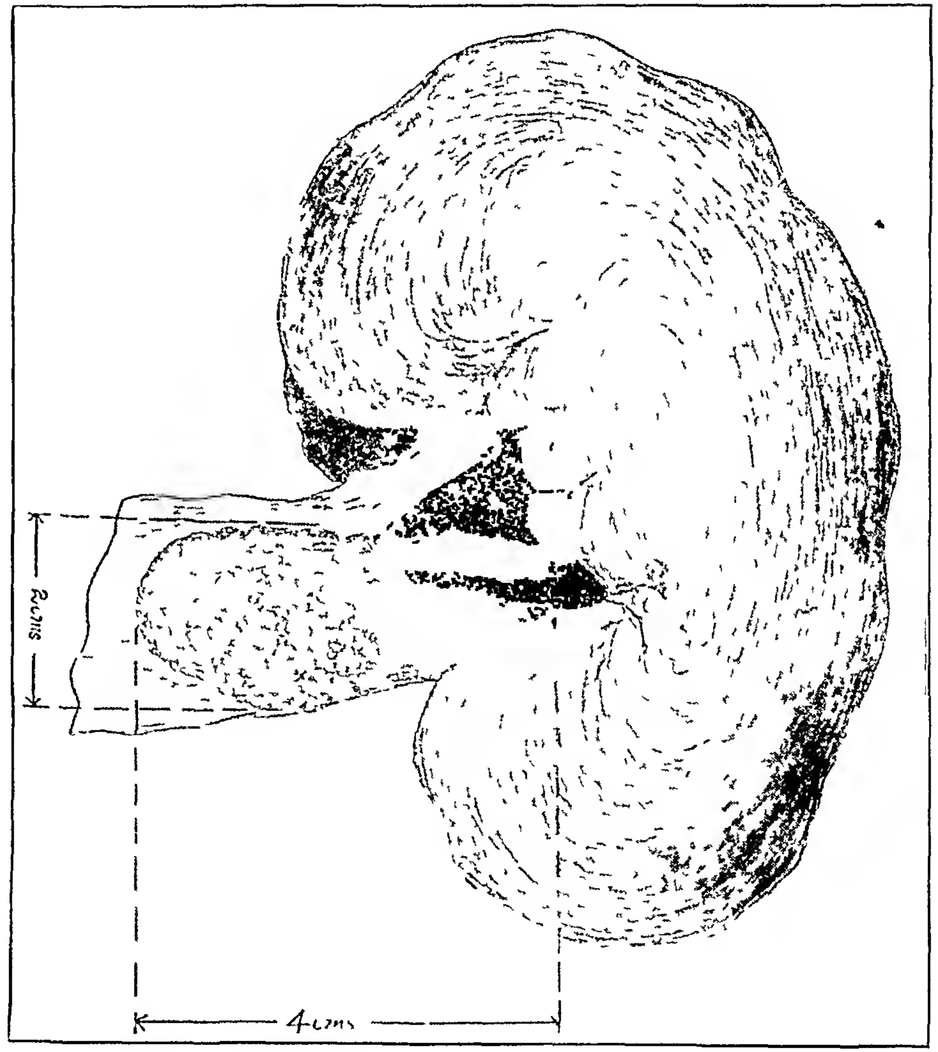

Fig 2—Sketch representing the tumor thrombus in the left renal vein

stroma (Fig 5) This arrangement of the tissue cells was best understood after a serial section study by which the relation of the blood vessels and stroma to the epithelium could be determined Such a study revealed a papillomatous structure, the thin-walled vessel of the rosette occupying the center of a villus, from which secondary radiating prolongations extended outward At the extreme upper limit of the papilloma stem proper only cross sections of cells with a little stroma not constantly present were noted Tangential sections of such papillae give the impression of rampant cell growth without definite

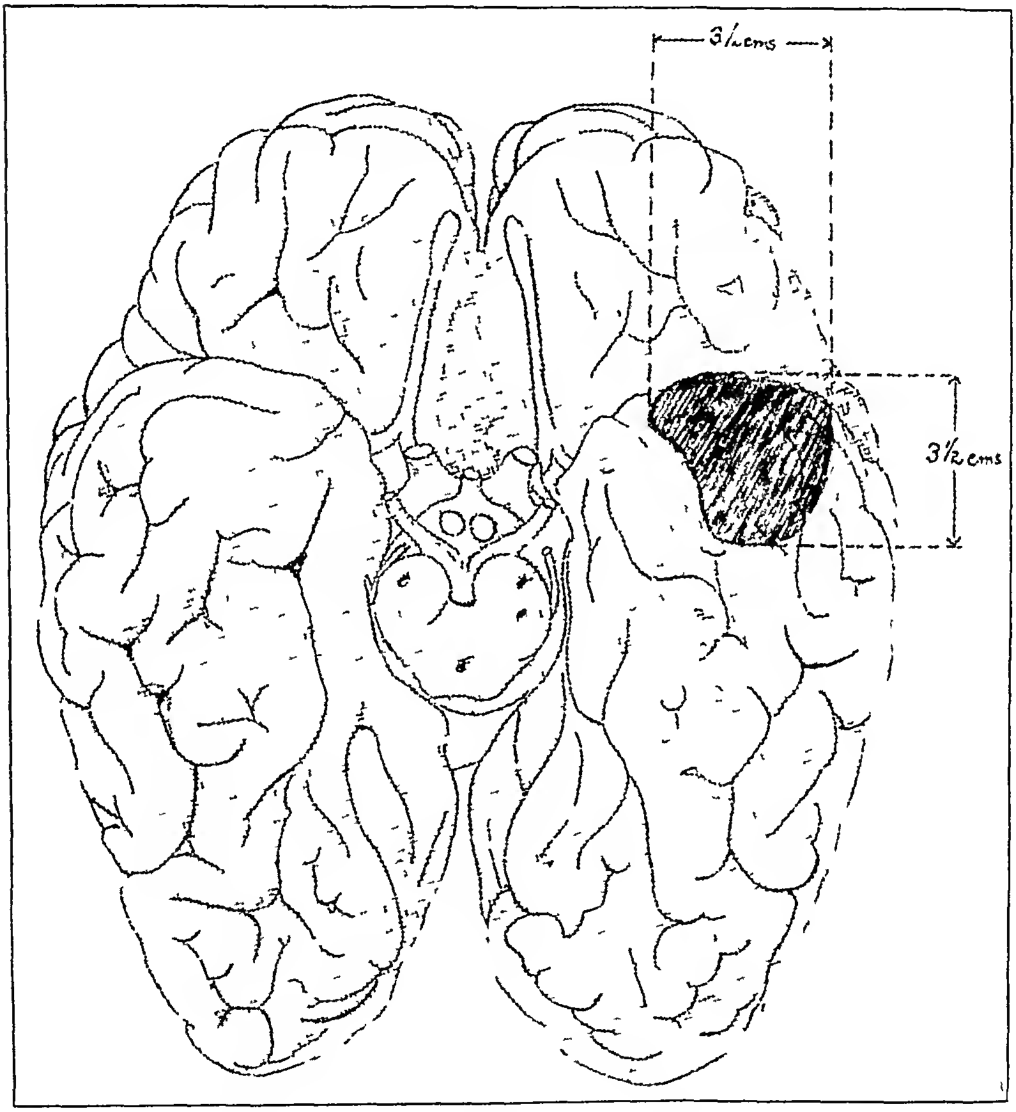

Fig 3—Diagrammatic sketch to locate the brain metastasis

arrangement, excepting for the slight grouping of cells into clusters of three or five which might be interpreted incorrectly, except after a serial section study[4] These areas were present in the tissues where the rosette structures were not definite, and had maximum dimensions varying between 0 5 and 1 5 mm Irregularly scattered throughout the tumor substance were necrotic areas, into some of which hemorrhage had occurred The necrosed tissues lay between

4 Le Count, E R The Genesis of Carcinoma of the Fallopian Tube, Etc, Bull Johns Hopkins Hospital, 1901, **12,** 55

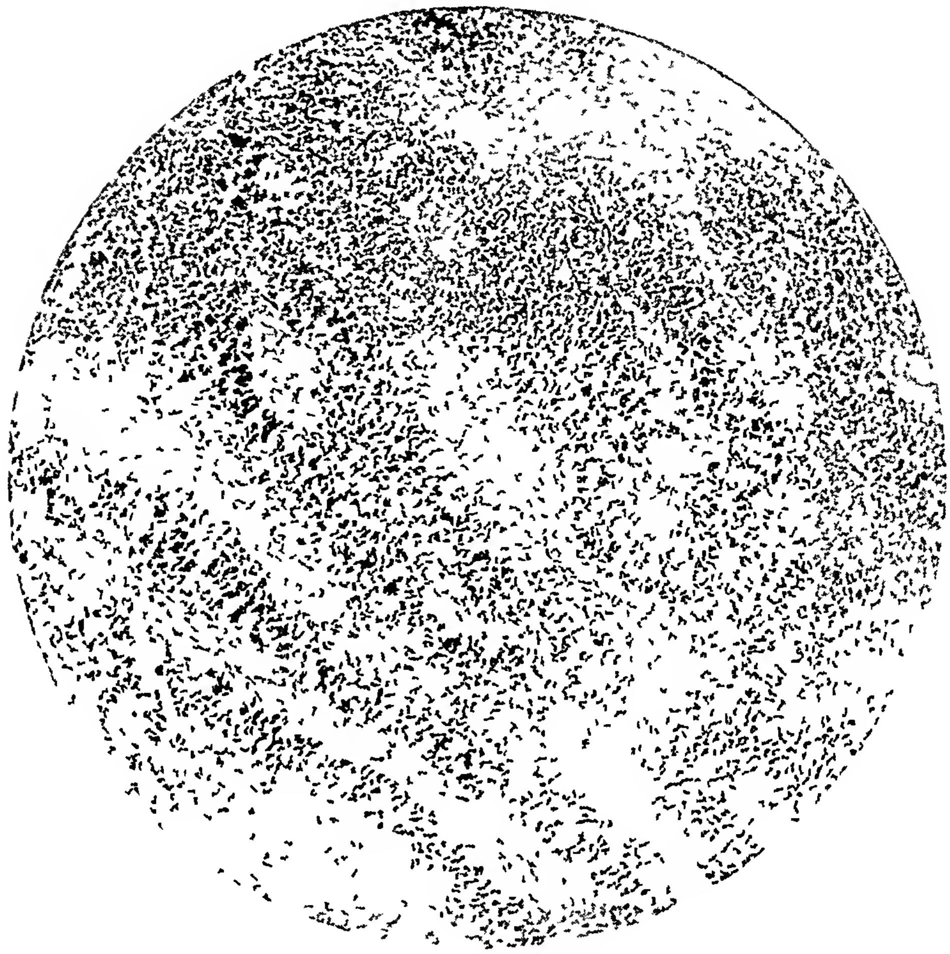

Fig 4—Photomicrograph illustrating the rosettes and papillae (× 70)

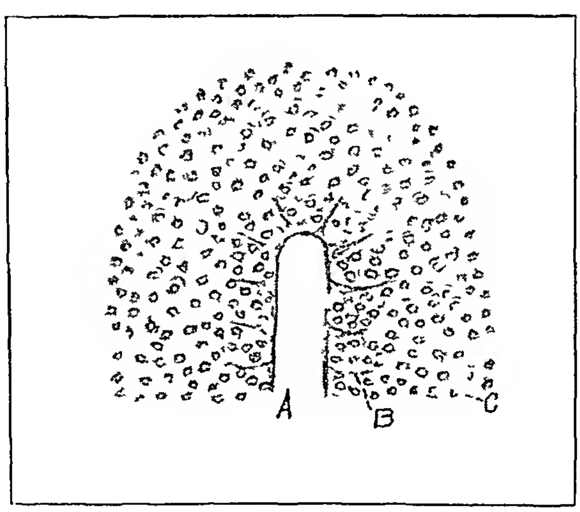

Fig 5—Diagrammatic sketch illustrating the structure of the papillary buds *A*, thin-walled vessel in papilloma stem, *B*, stroma, *C*, tumor cells

the peripheries of the papillae, corresponding therefore with the outer margin of the rosettes In sections they varied from those just discernible to others as large as a rosette The kidney substance in the region of the tumor was completely destroyed, while at the tumor edge the cells of the latter invaded the renal tissue, forming the structures described Certain groups of tumor cells were pigmented brown by the split products of the red blood cells that escaped from the blood vessels with the necrosis of the tumor tissue

Sections of the brain tumor showed a histologic structure similar in most respects to the tumor described in the kidney The cells were identical in appearance, and for the most part had a radial arrangement about well defined capillaries, forming rosettes as in the kidney Other areas of these cells, not so arranged, approximated 1 cm in diameter, while between the peripheral margins of adjacent areas were equally extensive regions of tissue necrosis, with only remnants of nuclei and cell structure remaining Some of these necrotic areas were from 2 to 3 mm in their maximum dimensions, and involved not only the tumor proper, but also regions of brain substance At the periphery of the tumor the growth of the tumor cells along the lymphatics might be noted where they appeared as small groups about the vessels, gradually encroaching on the brain tissue, causing its destruction and forming structures as heretofore described

This tumor, without doubt, was primary in the left kidney, and, classified according to the description, belongs to the malignant papillary tumors arising in the renal parenchyma Its early tendency to invade the blood vascular system is striking, and because of this its metastasis into the brain tissue is readily understood The absence of well developed metastases in other organs, however, especially the lungs, is of interest, particularly when the entire clinical picture is considered from a diagnostic standpoint The absence of positive urinary findings need not be taken seriously, especially since only two were reported during the eight weeks the deceased was under observation, and in all probability blood cells were present in the urine at some time during this interval In conclusion, emphasis may be placed rightly on the importance of thorough routine examination, both physical and laboratory, with the hope that in so doing accuracy in diagnosing such tumors clinically may be approximated

THE RELATIONSHIP OF THE TOXIC LYMPHOID HYPERPLASIAS TO LYMPHOSARCOMA AND ALLIED DISEASES *

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The dominant function of the lymphoid tissues is to arrest foreign substances brought to them in suspension and to manufacture phagocytic cells for the blood and tissue spaces In certain situations, notably the gastro-intestinal tract, the geographical intimacy between the lymphoid tissues and an absorptive surface of enormous dimensions would seem to indicate that the lymphoid cells were placed there primarily for purposes of filtration, restraining such foreign bodies as bacteria, and filtering their toxins That the lymphoid depots in question are a source of supply of wandering phagocytes cannot, of course, be denied, but that this function is subsidiary appears to be indicated by the fact that, in lymphatic leukemia, which is essentially a disease of the lymphoid hemopoietic system, the gastro-intestinal lymphoid follicles escape altogether, or exhibit a negligible degree of hyperplasia The regional lymph nodes, on the contrary, such as those of the neck, axilla and groin, are actively engaged in both directions, that is to say, in the process of filtration and in the formation of lymphocytic phagocytes

In addition to the lymphoid depots mentioned, there is an auxiliary system to be found in the form of small islands of lymphoid cells of rather wide distribution in the interstitial tissues of the thyroid, prostate, testicle, lungs, kidneys, liver and adrenal, in the subcutaneous tissues and serous membranes, and elsewhere These deposits are sometimes so small as to escape notice in the routine histologic examination of tissues, at other times they are provided with definite germinal follicles and are easily seen One is, nevertheless, apt to receive the impression that these lymphoid foci are functionally insignificant, and doubtless this is true They are, however, not infrequently brought into prominence in certain diseases characterized by hyperplasia of lymphoid cells, particularly in Hodgkin's disease and lymphosarcoma, while in the liver in enteric fever they undergo increase in size in com-

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* From the Pathological Laboratories of Bellevue Hospital, Director Dr Charles Norris

pany with the intestinal, mesenteric and splenic follicles, giving rise to the so-called focal necroses In lymphatic leukemia they seldom share in the process of hyperplasia

The spleen appears to occupy the same relationship to the arterial blood as the lymph nodes bear to the skin and mucous membranes The presence of lymphoid follicles in the spleen and their close connection with its vascular supply, is of itself an indication that, among other things, the organ is part of the body's filtration plant Other facts lend color to the view Thus, the frequent occurrence of sclerotic and degenerative changes in the splenic artery suggests that this vessel is engaged in the transportation of vitiated blood to the splenic substance, while the absence of corresponding changes in the splenic vein indicates that its blood has been partially purified in the spleen before being expelled and subjected to further detoxication in the liver

In addition, the spleen is a favorite site for separating bacteria and other parasites from the circulation, as shown by the experimental bacteremias,[1] and in the same way, it is sometimes possible to demonstrate malarial parasites in scrapings or sections from the splenic pulp after repeated examinations of the peripheral blood have failed to show them Still further confirmation is to be found in the presence of sclerotic infarctions in the spleen associated with healed or healing infective lesions of the heart valves, in which circumstances bacteria are transported during the active periods of infection from the endocardium to the splenic vessels where, acting primarily on the intima, they produce infective lesions characterized by thrombophlebitis and infarction

Moreover, the histology of the spleen is peculiarly adapted to purposes of filtration, the distensible sinuses lending themselves admirably to the temporary pooling of blood, so that the blood itself or the endothelial cells of the sinuses, or both, may deliberately exert lytic properties on alien cells deposited in the spleen Thus, metastasizing tumors rarely find hospitable lodgment in the spleen, even in those cases in which dissemination of tumor cells by the lymph or blood stream produces secondary growths in practically every other organ in the body Of 298 malignant tumors studied by myself at Bellevue Hospital,[2] the spleen was metastasized sixteen times, or in 5 3 per cent, and in practically every instance the secondary growths were small in both size and number In a single exception the spleen was riddled by metastases following neoplasmic thrombosis of the splenic vein and retrograde embolism to the venous sinuses In five cases of generalized tumor metastases the spleen was involved but once — a case of melano-

1 Bartlett and Ozarki Jour Med Research, 1917, **35**, 465
2 Symmers, D Am Jour Med Sc, 1917, **154**, 2255

matosis in which there were three secondary deposits — and yet, in all of these cases, the spleen must have been visited on innumerable occasions by tumor cells whose vegetative properties were no less exalted than in those which were delivered to and successfully inoculated in other tissues

Finally, it may be recalled that, in disturbances of the bone marrow, such as occur in myelogenous leukemia and Hodgkin's disease, fully formed myeloplaxes are not uncommonly discharged into the circulation and separated out in the splenic sinuses, a finding which has also been observed in experimental infection of certain lower animals by the bacillus of hog cholera, pyocyaneus and anthrax, and after repeated artificial hemorrhages [3]

THE REACTION OF THE LYMPH NODES TO IRRITATION

The lymph nodes are called on to deal with at least two varieties of extraneous material, namely, solid particles, such as coal dust and other pigments, the bodies of bacteria, cell débris and the like, and soluble irritants in the form of toxins derived from the skin and mucous membranes or formed in the lymph nodes by living micro-organisms The cellular reactions in the lymph nodes vary according to the nature of the foreign bodies offered to them for disposal In the case of insoluble particles, such as coal dust, the reaction consists in fibrotic changes in the interstitial framework, usually with, but sometimes without, corresponding numerical increase in the endothelial cells of the sinuses The lymphoid cells maintain a passive attitude, but, as time goes on and the sinuses become occluded by desquamated endothelium and pigment granules, or are encroached on by the growing connective tissues, the flow of lymph is impeded and the lymphoid cells suffer atrophy and diminution in numbers

In the case of bacteria the reaction in the lymph nodes differs with the nature of the invading parasite For example, the typhoid bacillus, which combines with the bacillus of tuberculosis and the spirochete of syphilis to form a group of micro-organisms expressing an inimical predilection for lymphoid tissues, acts on the lymph nodes in such fashion as to produce necroses, together with hyperplasia of endothelium and of lymphoid cells In the case of the tubercle bacillus, the most frequent change consists in the formation of tubercles, usually of the so-called epithelioid type, a reaction which is a deliberate attempt to limit the activity of a foreign body by erecting a structural barrier between it and healthy tissues At the same time the lymphoid tissues in the immediate vicinity of the tubercle, or even throughout the node,

3 Opie Am Jour Med Sc, 1904, **126**, 988, Pugliese Fortschr d Med, 1897, **15**, 727

undergo hyperplasia, representing a response to the action of toxins derived from the bacillus — a type of biologic phenomenon the significance of which was first clearly recognized by Weigert[4] who, on the basis of observations of this sort, postulated the doctrine of regenerative over-production of cells He advanced the view that physiologic structure and function depend on equilibrium maintained by the mutual restraint of cells, and that destruction of a cell or group of cells releases restraint to an extent sufficient to disturb the equilibrium of the remaining cells, in this way permitting them to exhibit abnormal proliferative energies and to produce new cells in abundant excess of those actually required to compensate for loss Hyperplasia, therefore, is not a direct, but an indirect result of irritation, the irritant serving to destroy cells and not to stimulate those that remain in the direction of regeneration The doctrine of regenerative overproduction finds a corollary in the process of paralytic and degenerative hypersecretion, which is of frequent occurrence in pathologic conditions For example, section of the corda tympani nerve results in focal degeneration and necrosis of the nuclei of the submaxillary gland, and this, in turn, is followed by abundant hypersecretion of saliva The same process is illustrated by various inflammatory reactions, notably the catarrhal lesions, which are attended by extensive degeneration of cells and by hypersecretion of mucus Even in physiologic conditions the process of degenerative hypersecretion is sometimes to be observed, the overproduction of milk by the lactating breast being accompanied by destructive changes in the cells of the galactiferous tubules It is apparent, therefore, that, in reacting to injury as well as in responding to physiologic demands, nature is apt to be prodigal not only of cells but of secretions as well

Weigert's doctrine of overproduction is abundantly illustrated, in fact, examples are far too numerous to permit of more than passing mention at this time Suffice it to recall the excessive regeneration of tubules in the lactating breast and in chronic interstitial mastitis, as well as in certain forms of adenomatoid hyperplasia of the thyroid, stomach, colon, prostate, liver and other organs In all of these conditions not only is the supply of new cells greatly in excess of the number lost, but the new cells constitute a menace, since they approach a type of architecture in which equilibrium between structure and function is unstable, and, unless every source of irritation is removed, growth is apt to proceed beyond the control of the body and a malignant tumor result The doctrine is likewise applicable to the lymphoid tissues, among which excessive regeneration of cells occurs in a variety of circumstances attended by the presence in the tissues

4 Weigert Verhandl d Gesellsch d Deutsch Naturforsch u Aerzte Part 1, September, 1896, 121

of toxic substances which act as irritants Thus, the injection of tetanus toxin into the sciatic nerve is followed by hyperplasia of the lymph nodes in the vicinity of the nerve trunk, and, in certain non-ulcerative malignant growths, hyperplasia of the regional nodes is not infrequently demonstrable microscopically, due, undoubtedly, to the absorption of irritant products In this connection, the experiments of Flexner[5] are of great significance He has shown, for example, that the injection of lymphotoxins in geese and guinea-pigs, when carried out over a long period, is followed by extraordinary hyperplasia of the lymph nodes throughout the body

Tuberculosis, however, furnishes the best examples of toxic lymphoid hyperplasia There is a form of tuberculous lymphadenopathy consisting of diffuse hyperplasia of lymphoid cells without any suggestion of tubercles, the establishment of the nature of the process depending on the detection of tubercle bacilli in the enlarged nodes, on the experimental reproduction of tuberculosis in susceptible animals following the injection of emulsified tissues, or on comparison with preceding or subsequent lesions in the same type of tissue in the same individual A case of this description occurred in a 6-year-old boy at the New York Hospital The patient presented an enormous mass on one side of the neck Removal and microscopic examination of the enlarged nodes showed tubercles in practically all of them Several months later the nodes on the opposite side became enlarged following an attack of diphtheria In these the only detectable change consisted in extensive and diffuse hyperplasia of lymphoid cells Neither tubercles nor tubercle bacilli were found in spite of an exhaustive attempt to learn the nature of the lesion, and whether it was a form of tuberculosis, or whether it was due to the absorption of toxic products from the diphtheritic membrane, was never satisfactorily determined

It is interesting to observe that tuberculosis is held to be responsible for a certain percentage of all cases of hyperplastic tonsillitis, a view which has been challenged by certain observers on the basis of failure to find tubercles in the enlarged tonsils In guinea-pigs, however, it has been found that injection into the tonsil of given strains of tubercle bacilli results in marked lymphoid hyperplasia, not alone in the tonsils, but in the regional nodes, and this without the formation of tubercles in either locality, tubercle bacilli, however, being demonstrable, by appropriate methods of staining, weeks or even months later It follows, I think, that certain cases of apparently simple hyperplastic tonsillitis in human beings might be ascribed to the same cause

5 Flexner Univ Penn Med Bull, 1902, **15,** 287

Finally, there is a variety of disseminated lymphoid hyperplasia[6] of tuberculous origin characterized by involvement of the lymph nodes throughout the body and by participation of the lymphoid structures of the stomach and spleen without the occurrence of tubercles in any of the localities named

In connection with the same general subject I may cite the case of a woman, 55 years of age, who, about a year prior to this report presented a mass on the right side of the neck that was about the size of an adult fist The growth projected into the side of the mouth, displacing the tonsil backward Both the skin and mucous membrane covering the mass were intact A portion of the growth was removed and sent to me for microscopic examination I returned a diagnosis of lymphosarcoma, based partly on the microscopic appearances and partly on the fact that Gram-Weigert and Levaditi preparations and sections stained by Hermann's method for tubercle bacilli were negative The patient was regarded by the surgeon as inoperable, and she was subjected to treatment by radium The growth disappeared completely In the light of this astonishing result I submitted the original microscopic preparations to two disinterested pathologists, both of whom concurred in the diagnosis of lymphosarcoma Whether the diagnosis was correct or not, however, is largely a matter of scientific interest, and does not modify the fact that the mass was a localized lymphoid hyperplasia, apparently of toxic origin, the cells growing with such rapidity as to jeopardize life

LYMPHOSARCOMA

In the necropsy service at Bellevue Hospital in the past ten years there have been twelve cases of lymphosarcoma, which, taking into account the fact that our necropsy records exceed 5,500, indicates that the lesion is not a common one Eleven of the twelve cases occurred in males In six of the cases the growth was first observed in the cervical lymph nodes, in three the changes observed postmortem suggested that the process commenced in the lymphoid remains of the thymus gland, and the remaining three in the small intestine Some of the cases exhibited features which are considered worthy of presentation at length

Lymphosarcoma is essentially a growth of regional distribution, although occasionally it displays an extraordinary faculty for bringing about diffuse lymphocytic infiltration of remote viscera At other times it is associated with variable numbers of lymphoid nodules in such organs as the kidney, liver and suprarenal capsule where, in normal conditions, lymphoid cells are present only in the form

6 Coley and Ewing Proc New York Path Soc, New Series, 1909, **10,** 145

of foci so minute as scarcely to attract notice on microscopic examination To the unaided eye these nodular "metastases" in lymphosarcoma appear to be well circumscribed, but, on microscopic examination they fade into the surrounding tissue spaces in such gradual fashion as to indicate hyperplasia of pre-existing lymphomas rather than foci springing from transplanted cells derived from a remote growth

Anatomically, the lymphosarcomas are divisible into five groups, one (*a*) characterized by diffuse infiltration of tissues, more especially of paired organs, a second, (*b*) involving regional collections of superficial lymph nodes, a third, (*c*) implicating the lymphoid structures of the thorax, notably the remnants of the thymus gland and the lymph nodes at the root of the lung, a fourth, (*d*) the lymphoid tissues of the abdomen, including the stomach, intestine, spleen and lymph nodes, and, fifth, (*e*) there is a variety of leukosarcoma, described by Sternberg, which is characterized by lymphoid tumors in unusual situations, the growth pouring its lymphocytes into the blood in such quantities as to constitute a leukemia In this category belongs, also, I believe, the disease commonly known as chronic lymphatic leukemia

SYMMETRICAL LYMPHOSARCOMA

(*a*) *Mikulicz' Disease* —The implication of paired organs by lymphosarcoma is well shown by a lesion first fully described by Mikulicz It usually commences as an infiltrative overgrowth of the lymphoid cells normally existing in the stroma of the lacrimal glands, and is manifested by symmetrical enlargement of the outer two-thirds of the upper eyelids, followed by symmetrical enlargement of the parotid and submaxillary glands In the case originally described by Mikulicz the histologic changes were characteristic of lymphosarcoma, small collections of closely packed lymphoid cells being supported by delicate trabeculae of connective tissue Precisely the same combination of symmetrical lacrimal, parotid and submaxillary adenopathy has since been observed in lymphatic leukemia, the change depending on diffuse infiltration of lymphocytes

(*b*) *Symmetrical Conjunctival Lymphosarcoma* — A condition related to Mikulicz' disease is to be found in bilateral lymphosarcoma of the conjunctival lymphoid follicles — a lesion which does not appear to have been described previously The case which came under my observation was that of a man, 37 years of age The palpebral conjunctiva of the right eye was greatly swollen and thrown into folds which caused eversion and depression of the lower lid and encroached on the ocular conjunctiva to the lower level of the cornea The conjunctiva of the opposite eye was similarly affected, but to a less extent

Microscopic examination revealed the histologic picture of lymphosarcoma with neoplasmic infiltration of the tissues of the lid

(*c*) *Symmetrical Lymphosarcoma of the Paired Viscera* — The tendency of lymphosarcoma to bring about symmetrical neoplasmic infiltration of certain tissues is shown by bilateral invasion of the mammae, ovaries, testicles, suprarenal capsules and certain paired members of the bony system — a remarkable capacity which it shares with the so-called chronic lymphatic leukemia and its alleged companion lesion, pseudoleukemia [7] One of the most striking of all the symmetrical infiltrations in lymphosarcoma, however, is to be seen in the kidneys, in which vast hordes of tumor cells penetrate the connective tissue framework and produce enormous enlargement of the organs without correspondingly extensive or severe microscopic alterations in the tubular epithelium or very profound disturbances in the excretory function of the kidney Here, again, lymphosarcoma is not alone in producing changes of the sort described, since an identical lesion exists in the kidney in the so-called pseudoleukemia, having, in fact, been observed by Cohnheim in his original case [8]

Three examples of symmetrical lymphosarcomatous infiltration of the kidneys occurred in the Bellevue Hospital necropsies, in two of which the original focus of growth was apparently in the lymphoid remains of the thymus gland, while the third was associated with lymphosarcoma of the small intestine In the Bellevue cases the several clinical histories and necropsy protocols have been abbreviated as much as is consistent with an intelligible presentation, and are as follows

CASE 1 —The patient was a man, aged 26, a butcher by trade, who was admitted to the hospital complaining of shortness of breath He said that three weeks before admission he suddenly became short of breath and subject to a severe cough attended by pain in the chest and expectoration On admission it was noted, in addition, that the fingers were cyanotic, that the subcutaneous tissues were edematous and that ascites was marked Repeated examinations of the sputum for tubercle bacilli were negative The temperature was normal throughout The urine showed a trace of albumin and hyaline and granular casts The blood contained 13,000 leukocytes, of which 34 per cent were lymphocytes Physical examination revealed slight bulging and dulness over the lower right side of the chest and dulness beneath the right infraclavicular region and between the scapulae The area of cardiac dulness was increased, the apex beat was neither visible nor palpable and the heart sounds were muffled

Necropsy (1483) —The body was that of a man, 26 years of age On section the subcutaneous tissues were universally edematous The peritoneum was thickened and opaque and enclosed several liters of turbid, yellowish fluid On removing the sternum the anterior mediastinum was found to be occupied by a growth which, in a general way, conformed to the shape of the thymus gland, and measured 9 by 13 by 10 cm The mass extended downward as far as the level of the auriculoventricular groove and upward to within a short

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7 Fabian Beitr z path Anat u allg Path, 1912, **53**, 491
8 Cohnheim Virchows Arch f path Anat, 1865, **33**, 451

distance of the lower border of the thyroid gland Laterally it infringed on the root of the left lung, bands of tumor tissue infiltrating the connective tissue planes along the larger bronchi for a distance of several centimeters On section, the growth was made up of yellowish white tissue which was divided into lobules of variable size by bands of dense, whitish connective tissue The substernal, peribronchial, peritracheal and lower cervical lymphnodes were enlarged, discrete, the largest approximating the size of a cherry, and, on section, the cut surface was bulging

Heart The pericardium contained about 200 c c of turbid, yellowish fluid with fibrin flocculi, and both layers were covered by fibrinous exudate The heart was greatly increased in size and the epicardial fat was diffusely infiltrated by grayish yellow tissue similar to that of the growth in the region of the thymus gland The walls of both ventricles were enormously thickened, rigid, and largely replaced by grayish yellow tumor tissue, islands of reddish musculature being preserved at scattered intervals The pleura covering the parietal and diaphragmatic surfaces of the right lung measured 0 5 cm in thickness and was adherent to the chest wall, pericardium, and diaphragm through the medium of infiltrated tumor tissue

Kidneys The kidneys were massively enlarged and weighed together 1,300 gm Each measured 17 by 8 5 by 8 cm The cortices were unusually broad and grayish yellow in color, standing out in marked contrast to the dark red pyramids On section the cut surface was smooth, pale, the substance bulging and glazed The mesenteric and retroperitoneal nodes were enlarged to the extent of from 1 to 4 cm

Anatomic Diagnosis—Lymphosarcoma of the anterior mediastinum corresponding to the lymphoid remains of the thymus gland, lymphosarcomatous infiltration of the peribronchial connective tissues of the left lung and of the parietal pleura of the right lung, of the pericardium and both ventricles of the heart, serofibrinous pericarditis, massive symmetrical lymphosarcomatous infiltration of the kidneys, lymphosarcomatous hyperplasia of the substernal, peritracheal, peribronchial, lower cervical, mesenteric and retroperitoneal lymph nodes

Microscopic Findings—Microscopic examination of the growth in the region of the thymus showed the presence of innumerable large and small islands of lymphocytes separated by irregularly distributed bands of fibrous tissue The lymphocytes in the islands showed no arrangement comparable to the delicate alveolar network so frequently seen in lymphosarcoma, but were closely packed in sheetlike arrangement The connective tissue planes of the heart were richly infiltrated by tumor cells, the intervening muscle fibers being atrophied or completely destroyed and replaced by broad sweeps of lymphocytic cells The connective tissues of the cortex of the kidneys were invaded to an extraordinary degree by lymphocytes, the tubules being widely separated and the glomeruli surrounded The tubular epithelium was granular and swollen The medulla was free The architecture of the lymph nodes was completely lost and replaced by dense, diffusely arranged lymphocytes which infiltrated the capsule and could be seen streaming off into the surrounding tissue spaces The other viscera revealed no microscopic changes of note

Case 2—The patient was a boy, aged 17, who, on admission to the hospital, said that two weeks previously he suddenly became short of breath and was seized by dull, constant pain in the upper part of the chest, attended by cough and expectoration The urine contained a trace of albumin, but no casts Frequent examinations of the sputum for tubercle bacilli were negative The sputum was blood tinged Both legs were edematous and the face and neck were cyanotic Physical examination of the chest showed marked flatness extending from the clavicles downward, and thoracentesis was attended by withdrawal of enormous amounts of blood tinged fluid At this time the heart sounds were clear The abdomen was distended by fluid

Necropsy (2836) —The body was that of a boy, 17 years of age The abdomen was prominent and, on section, released a large amount of faintly blood tinged fluid Both lower extremities were edematous On opening the thorax both pleural cavities were found to contain large quantities of slightly blood tinged fluid, compressing the lungs, which were displaced upward Lying in the anterior mediastinum corresponding to the position of the thymus gland was a large, pale or yellowish, firm mass which extended upward as far as the lower level of the neck and downward in front of the pericardium to the level of the auriculoventricular groove

Heart The pericardium was distended by a large amount of bloody fluid The parietal pericardium was thickened, and strewn over the visceral layer was a collection of reddish, shaggy, fibrinous exudate The heart muscle in the upper part of the left ventricle was fleshy in appearance

Kidneys Both kidneys were increased in size, measuring 15 by 10 by 8 cm, weighing together 1,040 gm The form was well preserved and the surface was extremely pale, the cortex broad, fleshy, and the markings obscured

The retroperitoneal and lower cervical lymph nodes were slightly enlarged The bone marrow presented numbers of scattered, whitish areas

Anatomic Diagnosis—Lymphosarcoma of the anterior mediastinum, corresponding to the region of the thymus gland, lymphosarcomatous infiltration of both kidneys, lymphosarcomatous hyperplasia of the cervical and retroperitoneal lymph nodes and of the pericardium and the superficial muscular planes of the left ventricle of the heart, hemorrhagic serofibrinous pericarditis, ascites, bilateral hydrothorax

Microscopic Examination—The histology of the growth found in the anterior mediastinum in the position of the thymus gland showed a scanty connective tissue framework of irregular distribution, in the meshes of which were enormous numbers of closely packed lymphoid cells The architecture of the lymph nodes was entirely obscured by diffuse overgrowth of identical cells The epicardium was covered by a thick layer made up of a superficial stratum of fibrin, below which was a quantity of richly vascularized granulation tissue densely sown with lymphoid cells Below this, in turn, was a zone composed exclusively of lymphoid cells, running downward from which into the intramuscular planes of the heart was a rich infiltrate, which ceased however, a few millimeters beneath the surface The bone marrow was richly strewn with lymphocytes

From the pathologic standpoint the two cases are interesting as emphasizing the occurrence of massive lymphosarcomas on the basis of the lymphoid remnants of the thymus gland, the growths giving rise, clinically, to detectable signs of intrathoracic pressure, including changes in the pericardium due to neoplasmic infiltration and embarrassment of the heart's action from a like cause The massive symmetrical infiltration of the kidneys is likewise interesting, particularly in view of the few changes referable to the secretion of urine

Case 3—In a third case encountered at Bellevue Hospital the patient, a man, aged 56, was admitted with the classical signs of cardiac decompensation, death being due to croupous pneumonia The urine contained a trace of albumin and a few hyaline and granular casts Beyond this the clinical history contained nothing of interest in the present connection At necropsy the middle of the jejunum presented two infiltrated, whitish elevations, 4 cm in diameter that extended around the intestine in bracelet fashion They were separated from one another by several centimeters of healthy mucosa A similar circumferential infiltrated band, 1 cm in diameter, was found in the

middle of the ileum, the center of the band, corresponding to the mesenteric attachment, being ulcerated

Kidneys The kidneys were enlarged and weighed together 630 gm They were yellowish white and, on section, the cortices were broadened and the markings were obliterated by cream colored tissue Numerous minute whitish specks were visible in the cortex

Anatomic Diagnosis—Lymphosarcoma of the small intestine, symmetrical infiltration of the adrenals and kidneys, lymphosarcomatous foci in the liver

Microscopic Examination—The histology of the growth in the intestine showed scattered areas of superficial ulceration and great thickening of the wall due to infiltrating lymphocytes The kidneys displayed enormous numbers of lymphocytes invading the intertubular spaces from cortex to pelvis The malpighian follicles and tubular epithelium appeared to be well preserved In the liver were innumerable minute lymphocytic foci, most of them lying in the connective tissue at the periphery of the lobules The adrenals revealed large numbers of lymphocytes arranged in islands or scattered diffusely through both cortex and medulla

In all of the three cases just synopsized the kidneys exhibited remarkable increase in size due to infiltration of hordes of tumor cells in the connective tissue framework, with or without attendant granular changes in the epithelium of the convoluted tubules, while the urinary changes were insignificant It is not at all clear why a lymphosarcoma in such a remote locality as the upper thorax, or even in the intestine, should bring about diffuse symmetrical invasion of one or more sets of organs in distant parts The only possible explanation seems to me to be that, in these circumstances, tumor cells are displaced at intervals from the parent growth and filtered out as a result of the presence in the recipient tissues of a chemotactic force, since, in the very nature of things, it is hardly conceivable that the resident lymphomas could occasion such widespread hyperplasia In expressing this predilection for the paired viscera the lymphosarcoma is not alone The so-called Krukenberg tumor, which is a primary carcinomatous growth springing from the parietal cells of the fundus glands in the stomach, commonly causes diffuse symmetrical invasion of the ovaries, and the same selective action is true of certain tumors which metastasize the suprarenal capsules, while the kidneys themselves are occasionally the seat of symmetrical metastases from tumors of the connective tissue series other than the lymphosarcomas

PSEUDOLEUKEMIA AND ALLIED CONDITIONS

Shortly after Virchow described lymphatic leukemia, Cohnheim[8] recorded a case which presented identical anatomic characteristics without changes in the blood, and for this disease he suggested the name of pseudoleukemia The designation has since been misapplied in various quarters and employed synonymously with Hodgkin's disease, from which, however, pseudoleukemia is readily distinguished on microscopic

examination In Cohnheim's case the patient was a man, aged 24, who suffered from anorexia, vomiting and repeated attacks of epistaxis The leukocytes were diminished in number At necropsy, in addition to enlargement of the cervical, inguinal and retroperitoneal lymph nodes, the spleen was found to be greatly enlarged, measuring 25 by 17 by 8 cm, and the pulp was richly infiltrated by lymphoid cells The kidneys were also increased in size, measuring 17 by 6 by 5 cm, and were infiltrated by lymphoid cells from cortex to pelvis

In addition to the variety of pseudoleukemia described by Cohnheim, a related lesion of the gastro-intestinal lymphoid structures has been recognized As far as I have been able to learn, the gastro-intestinal form is rare, only twelve cases having been found in the literature to date [9] The lesion is characterized by extraordinary hyperplasia of the gastro-intestinal lymphoid structures, myriads of enlarged follicles stretching from the cardiac end of the stomach to the anal margins, causing great thickening and rigidity throughout The individual follicles vary in size, and are so closely packed as scarcely to exhibit a hair's breadth between them The thoracic and superficial lymph nodes are usually involved, but not nearly in the same relative proportions as the follicles in the stomach and intestine The abdominal nodes, however, are apt to show marked changes The spleen is almost invariably enlarged, often approximating the splenomegaly of lymphatic leukemia The lymphoid cells in the blood are normal or approximately so—a fact which permits instant differentiation between the true and the so-called pseudoleukemia Anatomically, the gastro-intestinal lesion in question belies the title of pseudoleukemia to the extent that, in true lymphatic leukemia, the lymphoid structures of the gastro-intestinal tract rarely, if indeed they ever, undergo a degree of hyperplasia even remotely comparable to that just described In fact, in nineteen cases of chronic lymphatic leukemia of which I have records, the gastro-intestinal lymphoid structures were practically unchanged

In view of the extremely vague relationship of pseudoleukemia to lymphatic leukemia, and because of the anatomic distribution of the changes in the lymphoid apparatus in the so-called pseudoleukemia, and because of the fact that identical or related changes are encountered in the same situations in lymphosarcoma, I am of the opinion that pseudoleukemia should be discarded as a misleading and inappropriate designation, and that the lesion so named should be included among the lymphosarcomas

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9 Symmers, D The Archives Int Med, 1909, **4**, 218, Shoemaker New York Med Jour, Jan 1, 1910

Chronic Lymphatic Leukemia — Chronic lymphatic leukemia is a disease of the lymphoid system characterized by widespread and practically simultaneous enlargement of certain groups of lymph nodes, notably those of the cervical and axillary regions, the peribronchial nodes, and the spleen It is attended by enormous preponderance of lymphocytes in the blood, the cells being poured into the circulation from the hyperplastic lymph nodes, by the presence of huge numbers of infiltrating lymphocytes in the blood vessels and lymph spaces throughout the body, and by enlargement of the splenic follicles and diffuse infiltration of the pulp, the sinuses sometimes being so crowded with lymphocytes as to constitute lymphoid thrombi How much of the latter is due to the formation of lymphoid cells in the splenic follicles and how much to deposition from the blood, is impossible to say The liver is almost always greatly increased in size, its sinusoids are strewn with lymphocytes and circumscribed lymphocytic foci are present at frequent intervals Finally, the bone marrow, which, in normal circumstances, is practically devoid of lymphocytic foci, is almost completely replaced, myriads of lymphocytes occupying the marrow spaces, choking and distending the capillaries In a word, lymphatic leukemia is primarily a disease of the lymphoid system, and the blood stream, viscera, and bone marrow are secondarily infiltrated by cells identical with those encountered in the lymphosarcomas — all of which is in keeping with the conception of a primary neoplasm of the lymph nodes Reasoning by analogy with generalized toxic lymphoid hyperplasia in tuberculosis, it appears to me that chronic lymphatic leukemia may well represent an autonomous process due to a self-perpetuating lymphotoxin origin, that it belongs to the category of lymphosarcomas, and is an example of the applicability of Weigert's doctrine of regenerative overproduction The interpretation of lymphatic leukemia as a neoplasm attended by circulating metastases is substantiated by Sternberg's[10] leukosarcoma —a disease characterized by the presence of multiple lymphoid tumors, the cells of which are poured into the blood in such numbers as to constitute a true leukemia It is also confirmed by Ellermann's[11] observation that definite lymphoid tumors not infrequently develop in different situations in chronic lymphatic leukemia in both man and fowl

SUMMARY AND CONCLUSIONS

1 In view of the fact that one of the principal functions of the lymph nodes is that of a filter, it is reasonably to be assumed that, in a great variety of circumstances, the nodes are subjected to the destructive action of irritants, not only in the forms of solid bodies, such as

10 Sternberg Beitr z path Anat u Allg Path, 1905, **37**, 437

11 Ellermann Jour Am Med Assn 1917, **69**, 500

bacteria, but as soluble substances of many descriptions In the case of bacteria, the reaction in the lymph nodes differs with the type of micro-organism and is shown by simple phagocytosis and by regenerative and necrotic lesions, including, in the case of the tubercle bacillus, definite attempts to limit the sphere of activity of the invading parasite by the interposition of a mechanical obstacle in the form of a tubercle The reaction to soluble poisons is different, as shown, for example, by diffusion of the toxin of the tubercle bacillus, which is followed by hyperplasia of lymphoid cells, sometimes to a limited extent, at other times involving groups of lymph nodes, at still other times including practically all the lymphoid tissues of the body

Since the lymphoid tissues are so frequently exposed to the action of bacterial toxins and irritants brought to them in solution from absorptive surfaces of vast extent, and since, in these circumstances, they so often display a definite tendency to respond to irritation by hyperplasia of their cellular constituents, I think it not improbable that a like reaction is to be held responsible for the inception of certain types of disease characterized by overgrowth of lymphoid cells, local or general If the irritant is withdrawn after the lapse of a reasonable interval of activity the cellular reaction in the lymph node ceases and the hyperplastic process is withdrawn If, however, the irritant continues to act it appears to be inevitable that the cellular response will also continue Finally, a time is to be expected at which, either as a result of the activity of the same irritant, or, more probably, as the result of the formation of a self-perpetuating toxin in the lymph nodes concerned, the reaction is converted into a process characterized by indefinite hyperplasia

In the absence of a better explanation, this, I think, is a not illogical method of accounting for the origin of the lymphosarcomas and for similar otherwise inexplicable lesions of the lymphoid system, including not only certain localized lymphoid hyperplasias, but chronic lymphatic leukemia, pseudoleukemia and the like

2 Chronic lymphatic leukemia and its companion lesion, pseudoleukemia, together with the familiar examples of lymphosarcoma, present many clinical and anatomic changes in common The histologic alterations are closely akin, in fact, in many instances, they are indistinguishable one from the other It is simpler and more natural, I think, to correlate these lesions than it is to strain at the impractical and artificial task of attempting to separate them into clinical and anatomic entities For this reason I prefer to group them, together with Mikulicz' disease and the symmetrical conjunctival lymphosarcoma herein described, under the general heading of lymphosarcoma, as follows

1 Symmetrical superficial lymphosarcoma
- (a) Mikulicz' disease
- (b) Bilateral conjunctival lymphosarcoma

2 Leukemic lymphosarcoma
- (a) Chronic lymphatic leukemia
- (b) Sternberg's leukosarcoma

3 Regional lymphosarcoma
- (a) Cervical, axillary, inguinal
- (b) Thoracic
  - Thymic
  - Peribronchial
- (c) Abdominal
  - Gastro-intestinal
  - Intestinal
  - Mesenteric, retroperitoneal

4 Generalized lymphosarcomatosis

I wish to acknowledge my indebtedness to Dr Louis Shapiro of the intern staff of Bellevue Hospital for valuable assistance in abstracting a number of clinical facts from the hospital records

CHEMICAL CHANGES IN THE BLOOD AND URINE IN PROGRESSIVE MUSCULAR DYSTROPHY, PROGRESSIVE MUSCULAR ATROPHY AND MYASTHENIA GRAVIS *

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BOSTON

In May, 1916, we[1] reported the following findings in a case of progressive muscular dystrophy (1) low blood sugar, (2) low cholesterin content of the blood, (3) creatinuria, (4) a rise in the sugar content of the blood accompanied by a corresponding increase in muscular strength following treatment

We now submit further data[2] regarding the first patient, and figures for the glucose and cholesterin content of the blood and the creatin content of the urine in other cases of progressive muscular dystrophy, in progressive muscular atrophy, in myasthenia gravis, and — as controls — in conditions not accompanied by myasthenia of any form[3]

PERCENTAGE GLUCOSE IN THE BLOOD

Progressive Muscular Dystrophy
(1) 0 064 (2) 0 068
(3) 0 080

Myasthenia Gravis
(4) 0 0818 (5) 0 095

Progressive Muscular Atrophy
(6) 0 111 (7) 0 129

Chronic Arthritis
(8) 0 086 (9) 0 088
(10) 0 090 (11) 0 098
(12) 0 101 (13) 0 103
(14) 0 104 (15) 0 106
(16) 0 109 (17) 0 115
(18) 0 118 (19) 0 121
(20) 0 124 (21) 0 128
(22) 0 131 (23) 0 166

Chronic Endocarditis
(24) 0 103 (25) 0 105
(26) 0 107 (27) 0 110
(28) 0 127

Conditions Accompanied by Nephritis
(29) 0 123 (30) 0 123
(31) 0 133 (32) 0 146
(33) 0 159 (34) 0 204

Miscellaneous Conditions
(35) Hypertension 0 120
(36) Multiple sclerosis 0 110
(37) Hypotension 0 144†
(38) Tumor of the cord 0 140
(39) Psoriasis 0 090
(40) Tuberculosis of the spine 0 103
(41) Neoplasm 0 118
(42) Pernicious vomiting 0 094

Normal
(43) 0 115 (44) 0 129

Chronic Arthritis with Rapid Muscular Wasting ‡
(45) 0 119 (46) 0 120

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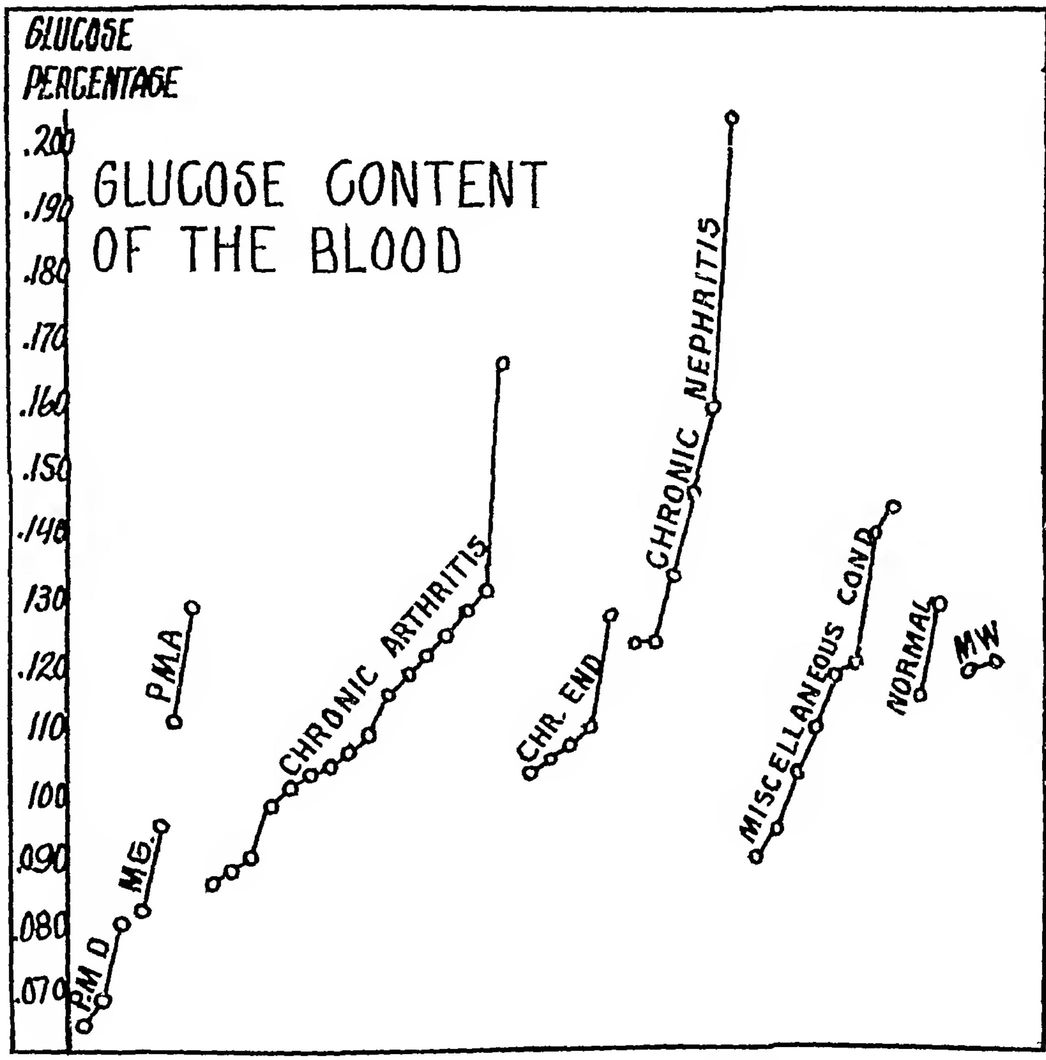
* From the Robert B Brigham Hospital

† In view of the fact that the epinephrin content of the blood is high in cases of hypotension (Bedford, E, and Jackson, H The Epinephrin Content of the Blood in Conditions of Low Blood Pressure and "Shock," Proc Soc Exper Med and Biol, 1916, **13**, 85), this low blood sugar, nearly high enough to give rise to glycosuria, is to be noted

‡ These are the same two cases reported in the earlier paper in which myasthenia developed as the result of marked muscular wasting secondary to rapidly progressing chronic arthritis

BLOOD SUGAR

The blood sugar in these cases (nephritis, progressive muscular dystrophy and myasthenia gravis excepted) falls between 0 09 and 0 13 per cent[6] Since but few of these patients were in good health, the figures are not offered as normal standards, but other investigators have found approximately the same range of values in normal cases[7]



Glucose content of the blood Each small circle indicates glucose content of the blood in one case Values for the same kind of disease are connected together with a line Abbreviations P M D = progressive muscular dystrophy, P M A = progressive muscular atrophy, M G = myasthenia gravis, Chr End = chronic endocarditis, M W = cases of chronic arthritis with muscular wasting

In the three cases of progressive muscular dystrophy the blood sugar is below the normal In the two cases of myasthenia gravis the blood sugar is a little below the normal In the two cases of progressive muscular atrophy blood sugar is normal

CREATINURIA

Large quantities of creatin were present[8] in the urine of the two patients with progressive muscular dystrophy The urine of the third (an outpatient) was not examined In Patient 1 the creatin excretion ran from 0 283 to 0 624 gm per day, the average for seven days being 0 465 gm In Patient 2, creatin ran from 0 356 to 0 608 gm, the average for eleven days being 0 503 gm per day

Of the two patients with progressive muscular atrophy, one showed 0 198 gm in a day's urine, the other an average of 0 130 gm per day

In one of the patients with myasthenia gravis (Patient 5) creatin was absent from the urine (the urine was examined every day for ten days) In the other (an outpatient) the urine was not examined

CHOLESTERIN

The cholesterin of the blood was low in all three cases of progressive muscular dystrophy The normal amount by the same method of analysis runs from 1 60 to 2 40 mg per gram of blood, and averages about 1 90 The percentage in these cases was

Case 1, 0 50 to 1 44, Case 2, 1 18, Case 3, 1 40

Blood cholesterin was not low in the patients with progressive muscular atrophy or in those with myasthenia gravis

BLOOD SUGAR AND IMPROVEMENT IN STRENGTH

In only one of the patients were we able to compare for long the glucose and cholesterin content of the blood with the improvement in muscular strength under treatment The blood sugar was as follows

	Blood Sugar Percentage
Oct 27, 1915	0 068
Nov 5, 1915	0 060
Treatment Begun	
Nov 16, 1915	0 074
Nov 23, 1915	0 091
Nov 30, 1915	0 081
Feb 21, 1916	0 095
June 20 1916	0 110
March 7, 1917	0 103

From the time treatment began the glucose showed an almost continuous rise There was a corresponding continuous gain in strength, and at the time of the last examination the patient had nearly completely regained his strength Under treatment for ten days the blood sugar of Patient 2 rose from 0 068 to 0 094 per cent The patient then moved to a distant city and the course of the disease could not be followed

ACIDOSIS

On account of the relationship of changes in the acid-base equilibrium to disturbances of the metabolism of sugar and creatin, the ammonia excretion in the urine was determined from day to day, but in none of our cases did it ever rise higher than 0 43 gm per day — a figure that is well within the normal limits

SUMMARY

In three cases of progressive muscular dystrophy were found (1) muscular weakness, (2) hypoglycemia, (3) hypocholesterinemia, (4) creatinuria, (5) normal ammonia excretion, (6) a rise of blood sugar in the treated patients with a parallel increase in strength

A comparison of the findings in three somewhat similar clinical conditions showed the following

	Blood Sugar	Creatinuria
Progressive muscular dystrophy	Low	Present
Progressive muscular atrophy	Normal	Present
Myasthenia gravis	Low	Absent

REFERENCES

1 McCrudden, F, and Sargent, C Hypoglycemia and Progressive Muscular Dystrophy, The Archives Int Med, 1916, **17**, 465

2 The technical details of the methods are described in our previous paper

3 Since Dr George Clymer, neurologist to the Robert B Brigham Hospital, who searched the community and found these myasthenic cases, is now in the national service abroad, we see no probability of obtaining any more cases in the near future

6 Blood sugar appears to remain fairly constant from day to day in any one individual (32) January 3 0 145 per cent , July 5 0 147 per cent , (33) August 20 0 159 per cent , August 23 0 159 per cent , (42) December 17 0 095 per cent , December 30 0 092 per cent

7 It is to be regretted that the very useful normal figures recently reported by Gettler and Baker (Jour Biol Chem , 1916, **25**, 211) were not controlled by duplicate analyses Some of the extreme figures would then be less open to suspicion

8 On a meat-free diet

THE NATURE OF THE PATHOLOGIC PROCESS IN PROGRESSIVE MUSCULAR DYSTROPHY

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BOSTON

In progressive muscular dystrophy we find (*a*) low blood sugar, and, following suitable treatment, a rise in blood sugar accompanied by an increase in strength, (*b*) creatinuria, (*c*) low cholesterin content of the blood — three independent testimonies of disturbed carbohydrate metabolism [1]

The condition of low blood sugar and parallelism between muscular strength and blood sugar speaks for itself

Creatin is not known to occur in the urine of men except as an accompaniment of some disturbance of carbohydrate metabolism It accompanies diabetes and starvation In dogs it accompanies hydrazin poisoning,[2] and phlorizin poisoning,[3] conditions resulting in hypoglycemia [4] In the rabbit, an animal in which hypoglycemia does not always follow hydrazin poisoning, creatinuria occurs only in those cases in which hypoglycemia does follow [5]

A low cholesterin content of the blood accompanies hypoglycemia,[1] a high cholesterin content is associated with hyperglycemia [6]

The glucose of the blood is the source of energy for muscular contraction Active muscle rapidly uses up glucose It may use more than six times as much as the resting muscle,[7] the venous blood from a faradized muscle may show only one half as much glucose as that from a resting muscle [8] Following severe muscular activity the blood sugar, even of the general circulation, may fall,[9] during the severe convulsions of tetanus it may fall to one third the normal [10] As the blood sugar falls, muscular power diminishes, but can be restored by glucose [11]

The dynamic potency of glucose has been especially clearly demonstrated for heart muscle The isolated heart perfused with Ringer's solution beats more and more feebly as its glycogen store becomes exhausted, and finally stops If glucose is added to the perfusion fluid this sugar is utilized[12] and the heart beats more powerfully and for a longer time [13] The utilization of glucose by muscle is a complicated physiologic process, it is lost if removal of the pancreas precedes isolation of the heart,[14] but can be restored by addition of pancreas extract to the perfusion fluid [14] The property is inherent in glucose alone, other sugars are impotent [15]

Besides muscular activity, certain other agencies may reduce the blood sugar — Addison's disease,[16] adrenalectomy,[17] dyspituitarism,[18] thyroidectomy and parathyroidectomy,[19] diphtheria toxin,[20] phosphorus poisoning,[21] and hydrazin poisoning,[4] and such agencies all produce profound asthenia In phosphorus poisoning and diphtheria toxemia the parallelism between severity of myasthenia and decrease in blood sugar is very marked,[22] and in successfully treated Addison's disease a parallelism between increase in strength and rise in blood sugar has been observed (Grote[10])

It is evident that the low blood sugar in progressive muscular dystrophy is a sufficient cause for the muscular weakness, the most striking symptom of the disease

As glucose passes from the blood into the tissues, the loss is made good from the glycogen store of the liver Replenishment is rapid and quantitative, the blood sugar being thereby maintained at a fixed level Hypoglycemia can result only from a failure of replenishment to keep pace with the needs, a loss of balance between supply and demand

Increased needs might result from increased sugar utilization or from loss through the kidneys We can rule out both There is neither the rise in temperature nor the increase in rate of heat loss that would accompany increased sugar catabolism, and the urine is sugar-free [1]

The cause of all forms of experimental hypoglycemia is a decreased rate of replenishment consequent on a diminished glycogen reserve After thyreoparathyroidectomy,[23] adrenalectomy,[24] diphtheria toxemia,[20] phosphorus poisoning,[25] hydrazin poisoning,[26] the liver and muscles contain far less than the normal quantity of glycogen, in some cases little or none

In progressive muscular dystrophy a rapid fall of blood sugar during the first twenty-four hours of starvation testifies to a scanty glycogen store in this condition too, in health the normal blood sugar level is tenaciously maintained throughout prolonged starvation [27]

The diminished glycogen reserve in experimental hypoglycemia results from impaired glycogenesis The carbohydrate ingested is not converted into glycogen (Porges[25]) The liver of the adrenalectomized animal, for example, does not store any glycogen even when glucose enough is ingested to increase the blood sugar fivefold (Mackenzie[24]) The glucose remains a long time in the blood,[28] and then, judging from the amount of "fatty degeneration" in these cases — adrenalectomy,[29] phosphorus poisoning,[21] hydrazin poisoning,[30] dyspituitarism[18] — it is probably changed to fat The rise in the respiratory quotient[31] and the increase in the fat content of the blood[32] lend further support to this hypothesis Such antagonism between fat storage and glycogen storage is well recognized [33]

The deposition of fat in the muscles[34] in progressive muscular dystrophy is evidence in this condition of a similar impairment of glycogenesis

Impaired glycogenesis may result from either liver or adrenal damage After phosphorus or hydrazin the result is due to liver destruction, after adrenalectomy or Addison's disease, to absence of epinephrin It is possible to tell which of the two—liver or adrenal—is at fault by the effect of epinephrin administration Normally, epinephrin[35] administration decreases the glycogen of the liver,[36] and thereby increases the glucose of the blood,[37] but it does not increase the blood sugar to the same extent after liver damage[38] During the first twenty-four hours after phosphorus poisoning while the liver is still intact, epinephrin increases the blood sugar, after the first twenty-four hours, liver injury precludes epinephrin activity[21]

The prompt and marked rise in blood sugar following epinephrin administration in progressive muscular dystrophy testifies to the adrenal rather than the hepatic origin of the disease[1]

The possibility that alkalosis plays a part in the etiology of progressive muscular dystrophy was suggested by the following facts connecting alkalosis, hypoglycemia and creatinuria

(*A*) *Alkalosis and Hypoglycemia* — (*a*) Alkali administration causes hypoglycemia,[39] it diminishes, and may even prevent epinephrin hyperglycemia and glycosuria[40] (*b*) Acid administration increases glycogenolysis, causes hyperglycemia, and augments epinephrin hyperglycemia (Elias[39]) (*c*) If a frog be kept in a slightly acid solution its store of glycogen diminishes, if in an alkaline solution, the glycogen store augments[41] (*d*) A base forming diet is more efficient as a glycogen former,[42] and gives a greater epinephrin glycosuria[43] than an acid forming diet (*e*) Epinephrin hyperglycemia is accompanied by a decrease,[44] and thyreoparathyroidectomy by an increase, in the alkali reserve of the blood[45]

(*B*) *Alkalosis and Creatinuria*—(*a*) In rabbits creatinuria follows administration of acid or an acid diet,[46] in which case the urine is always acid[47] (*b*) Alkali administration diminishes, and sometimes abolishes, the creatinuria of starvation[48]

But alteration in the acid-base equilibrium severe enough to produce hypoglycemia leads to marked changes in the reaction of the urine,[49] and such changes are not present in progressive muscular dystrophy — ammonia excretion is normal This is in harmony with the other evidence that the hypoglycemia of progressive muscular dystrophy is of endocrine origin The adrenals are not involved in the blood sugar variations brought about by changes in the acid-base equilibrium (Elias[39])

Another possibility? It is alleged[50] that epinephrin decreases, and that the internal secretion of the pancreas increases the rate of sugar oxidation, and that normally the two tendencies — inhibiting and stimulating — just balance. In accord with this hypothesis, epinephrin hyperglycemia is attributed to loss of balance in favor of — diminished glucose destruction — the suprarenal, and progressive muscular dystrophy might be attributed to corresponding loss of balance in favor of — increased sugar oxidation — the pancreas. But epinephrin does not decrease the rate of glucose destruction,[51] and all the evidence points to diminished glucose formation and not augmented glucose destruction as the cause of the hypoglycemia in progressive muscular dystrophy.

The facts indicate that the myasthenia of progressive muscular dystrophy is due to hypoglycemia, that the hypoglycemia and fatty infiltration are due to impaired glycogenesis, the carbohydrate of the food being probably changed largely to fat instead of glycogen, and that this impaired glycogenesis is the result of adrenal or other endocrine disease.

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THE EFFECT OF THYROID SECRETION ON THE EXCITABILITY OF THE ENDINGS OF THE CARDIAC VAGUS *[*]

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In an earlier communication[1] it was pointed out that, in the cat, after inducing secretory activity in the thyroid gland, either by stimulation of the cervical sympathetic nerves or by injection of small doses of epinephrin, there can be demonstrated an increased effectiveness of epinephin as a pressor agent In other words, thyroid secretion renders more excitable those sympathetic structures acted on by epinephrin in raising arterial pressure It was further shown that this effect is manifest only after a latent period, which may vary from about forty to sixty minutes, and that it is of considerable duration, having been observed for as long as seven hours

A number of investigators, notably Asher and von Rodt,[2] Ossokin[3] and Oswald[4] maintain that thyroid secretion increases the responsiveness of vagus terminations to electrical stimulation If this be true, thyroid secretion must be regarded as having a sensitizing effect on both true sympathetic as well as on parasympathetic (vagus) endings Their work, however, is open to three serious criticisms In the first place, all employed intact animals under anesthesia, under such conditions, owing to variations in the depth of anesthesia as well as to respiratory and vasomotor fluctuations, it is practically impossible to obtain uniform vagus responses to a given strength of stimulus Secondly, in some of the experiments (Asher and von Rodt[2] and Ossokin[3]), thyroid secretion is said to have been poured into the circulation as a result of stimulation of the laryngeal nerves, these nerves, according to recent work,[5] are in no way directly concerned with secretory discharge in the thyroid gland And finally, Oswald's results were obtained after injection of iodthyreoglobulin, a preparation which this author assumes is the active principle of the thyroid The variability and unreliability of effects which may be observed by employing dif-

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2 Asher, L, and von Rodt, W E Zentralbl f Physiol, 1912, **26**, 223

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4 Oswald, A Zentralbl f Physiol, 1915, **30**, 509, also Arch f ges Physiol, 1916, **164**, 506

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ferently prepared glandular extracts are too well known to require comment

It was the object of the present investigation to determine the effect of thyroid secretion on the excitability of the endings of the cardiac vagus under conditions which would meet satisfactorily the foregoing criticisms

METHODS

The methods employed were, in their essentials, similar to those used in the writer's previous work[1]

Cats were used in all the experiments During preliminary ether anesthesia, a tracheal cannula was inserted and to destroy the brain a perforation was made in the back of the orbit and a probe passed through it into the spinal canal beyond the level of the medulla Artificial respiration, carefully adjusted as to depth and rate and maintained by a motor-driven, air-blast interrupter, was now begun The cervical sympathetic nerves were dissected free from the vagus sheaths for 3 or 4 cm, ligated low in the neck and severed distal to the ligatures The depressor, when present as a separate nerve, was also cut The vagi were likewise isolated, ligated high in the neck and cut above the ligatures The probe was now again inserted through the orbit and the cord thoroughly destroyed to about the level of the second or third thoracic segment Usually, in the course of twenty minutes or half an hour, the blood pressure fell to a constant level at about 50 mm Hg An electric heating pad placed beneath the animal holder permitted the maintenance of a normal, or nearly normal, temperature

In cats pithed in this manner, the resulting rise in blood pressure after an injection of epinephrin varies directly with the amount injected Vasomotor and respiratory fluctuations are abolished The circulatory system responds with almost mathematical precision to repeated injections of a given dose

It was also found that, in these animals, repeated stimulation of the vagus with a given strength of stimulus results in uniform cardiac responses Both depth of depression of blood pressure and duration of inhibition are so constant that, over a period of hours, each of the series of curves can practically be superimposed on the preceding ones The result is the same whether right or left vagus is stimulated The pithed cat is, therefore, an excellent preparation for determining alterations in excitability of the cardiac vagus

A Sherrington electrode[6] was placed on one vagus and connected, through a signal magnet, with a tetanizing circuit The strength of stimulus employed approached as nearly as possible the threshold of excitability, which was determined at the beginning of each experiment[7] Less uniform, though comparable, results were obtained by employing an ordinary platinum stimulating electrode, the vagi being carefully moistened and protected between stimulations

A cannula inserted into the femoral artery was connected with a mercury manometer, sodium carbonate being used as anticoagulant Injections of epinephrin were made through another cannula placed in the femoral vein on the opposite side A slowly revolving kymograph was used to record the effects of epinephrin injections, a more rapidly moving one for the vagus responses

The epinephrin employed was the commercial "Adrenalin Chloride" of Parke, Davis & Co, and was fresh Immediately before each experiment it was diluted, 1 100,000, with distilled water The injections were made from a syringe

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6 Sherrington, C S Jour Physiol, 1909, **38**, 375

7 The pithed cat is such a delicate preparation that a measurably effective vagal stimulus frequently causes complete cardiac inhibition In experiments in which only slowing of rate occurred, the results were the same as where complete inhibition followed stimulation

with 1 c c barrel, graduated to fiftieths of a cubic centimeter A metronome, beating at intervals of one second, permitted delivery of the dose uniformly in successive injections Usually 0 2 c c were injected at the rate of 0 02 c c per second

For stimulating the cervical sympathetic nerves, a tetanizing current, rhythmically interrupted at the rate of about 25 or 30 times a minute, was employed, the nerve being laid over a platinum electrode The current was of such strength that it could comfortably be borne on the tip of the tongue and always caused maximal pupillary dilatation when the side with intact eye was stimulated

A time marker registering 30-second intervals during the epinephrin injections and 5-second intervals when vagus stimulations were recorded on the more rapidly revolving drum, served also as base line for zero blood pressure level

RESULTS

In cats prepared as described, repeated stimulation of either vagus over a period of several hours gives a uniform series of responses It is possible to obtain practically an identical curve with a given strength of stimulus from either right or left vagus At least five minutes were permitted to elapse between successive stimulations, in order that the heart might fully recover its irritability

After stimulation of the cervical sympathetic, even at a time when increased pressor response to a given dose of epinephrin gives evidence that there has been liberation of thyroid secretion, there is no significant alteration in depressor effect or duration of inhibition following stimulation of either vagus nerve It is therefore evident that, after the thyroid gland has poured forth its secretion in sufficient amount to sensitize the sympathetic structures acted on by epinephrin in raising arterial pressure, there is no demonstrable effect on the excitability of the endings of the cardiac vagus In the illustration are pictured the records of such an experiment, and in the table is given the complete protocol, which serves as an illustration for the series

Similarly, uniform vagus responses were obtained when, instead of stimulating the cervical sympathetic, a small dose of epinephrin (2 c c. of 1 100,000) was injected to induce secretory activity in the thyroid

It has been shown repeatedly[8] that an injection of epinephrin causes a temporary decrease in the irritability of the cardiac vagus, this effect in the cat, according to Langley, lasting only from one to two minutes The epinephrin injections in no way modified the effects of vagus stimulation in the present series of experiments An interval of at least eight minutes was permitted to elapse between any vagus stimulation and the preceding epinephrin injection To bring final proof, a number of experiments were performed in which, after taking the

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usual vagus controls, each cervical sympathetic was stimluated for five minutes No epinephrin was injected, yet, though presumably the thyroid glands had been vigorously stimulated, no alteration in the character of the vagus responses was observed over a period of several hours

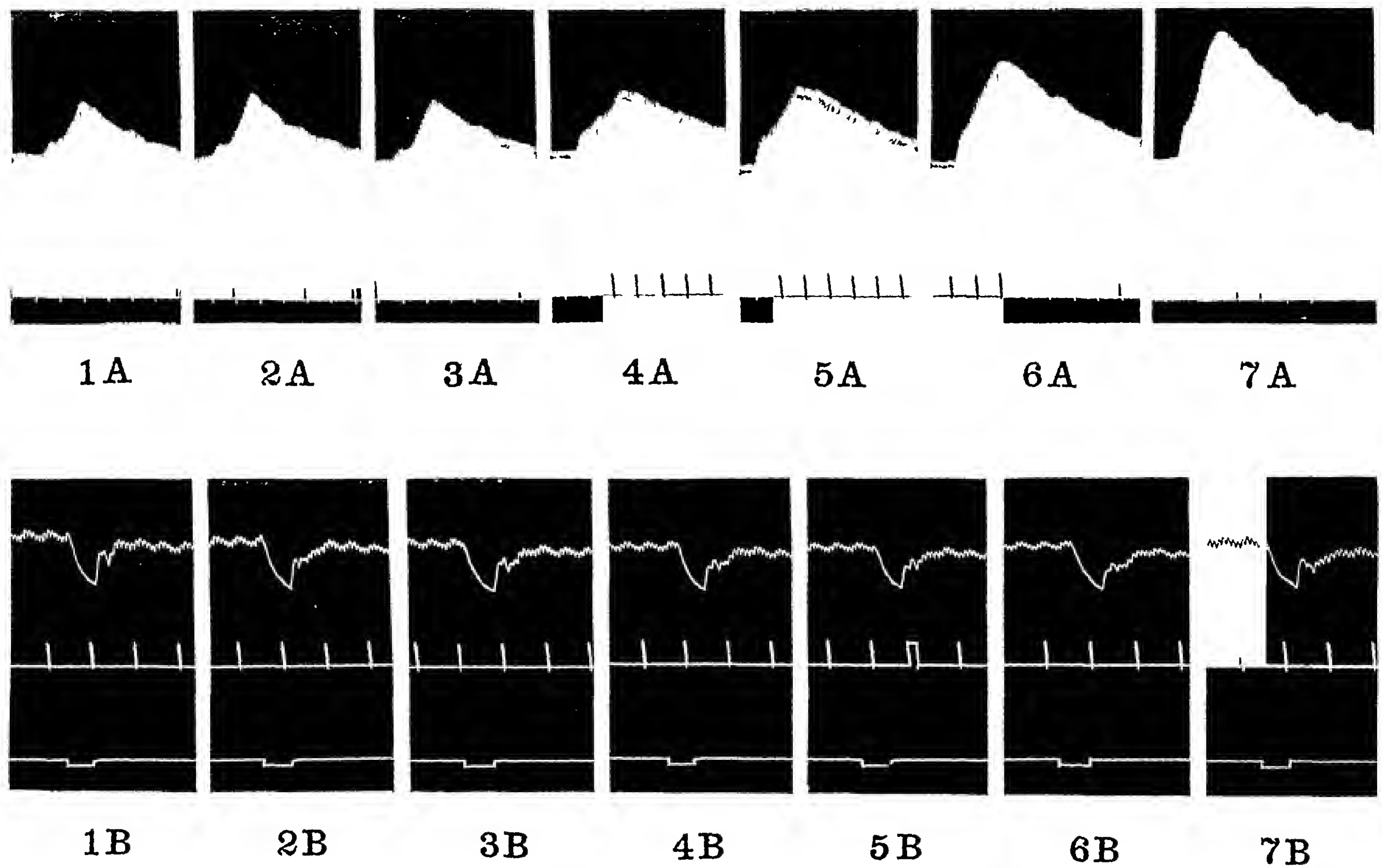
Illustrative Protocol (The records of this experiment, except Epinephrin Injection 6, are reproduced in the accompanying illustration)
Male cat, weight, 2 6 kg
9 20 Ether
9 25-9 45 Tracheotomy Pithed to midthorax, artificial respiration begun, vagi and sympathetics dissected out, ligated and cut, Sherrington electrode placed on right vagus, each epinephrin injection 0 2 c c, 1 100,000, injected at the rate of 0 02 c c per second The duration of each vagus stimulation was three seconds

Time	Procedure	Rise in Blood Pressure Following Epinephrin Injection (Mm Hg)	Effects of Vagus Stimulation	
			Depression of Blood Pressure (Mm Hg)	Duration of Cardiac Inhibition (Seconds)
10 25	Epinephrin injection 1	19		
10 31	Epinephrin injection 2	22		
10 40	Stimulation of right vagus		19	3 7
10 47	Stimulation of right vagus		19	3 4
10 51-10 57	Stimulation of left cervical sympathetic			
11 02	Epinephrin injection 3	22		
11 15	Stimulation of right vagus		19	3 7
11 50	Epinephrin injection 4	23		
12 00	Stimulation of right vagus		18	3 5
12 10	Epinephrin injection 5	29		
12 30	Epinephrin injection 6	34		
12 45	Epinephrin injection 7	38		
1 00	Stimulation of right vagus		17	3 7
1 15	Epinephrin injection 8	48		
1 23	Stimulation of right vagus		18	3 8
1 28	Stimulation of left vagus		18	3 9

SUMMARY

1 In cats pithed to midthorax, repeated stimulation of either vagus with a given strength of stimulus results in a uniform series of responses, both as to degree of depressor effect and duration of cardiac inhibition The pithed cat is, therefore, an excellent preparation for determining alterations in the excitability of the cardiac vagus

2 After inducing secretory activity in the thyroid gland, even at a



(The protocol of this experiment is given in the accompanying table)

The curves in the upper row (A) show rises in blood pressure after injection of 0 2 c c of epinephrin, 1 100,000 The time marker records 30-second intervals and is at zero blood pressure level

The lower tracings (B) show the effects of vagus stimulation The time marker records 5-second intervals and is at zero blood pressure level A signal magnet marks on the lowest line the three seconds during which the stimulus was maintained

1 A and 2 A, controls, taken 6 minutes apart (20 minutes after 2 A, the left cervical sympathetic was stimulated for 6 minutes) 3 A, 5 minutes after stimulation 4 A, 53 minutes after stimulation 5 A, 73 minutes after stimulation 6 A, 108 minutes after stimulation 7 A, 138 minutes after stimulation

1 B and 2 B, controls, taken 7 minutes apart (4 minutes after 2 B, the left cervical sympathetic was stimulated for 6 minutes) 3 B 18 minutes after s[illegible]

time when increased pressor response to a given dose of epinephrin gives evidence that there has been a pouring out of thyroid secretion, there is no significant alteration in depressor effect or duration of cardiac inhibition following stimulation of either vagus nerve

3 It is therefore evident that after the thyroid gland has liberated its secretion in sufficient amount to sensitize the sympathetic structures acted on by epinephrin in raising arterial pressure, there is no demonstrable effect on the excitability of the endings of the cardiac vagus

THE MAINTENANCE DIET IN DIABETES MELLITUS AS DETERMINED BY THE NITROGEN EQUILIBRIUM *

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In the treatment of diabetes mellitus there are two guiding principles which determine the caloric value of the diet In the first place, the quantity of carbohydrates, proteins and fats offered the patient must be within his carbohydrate tolerance, that is, the diet must be so regulated that the urine remains sugar-free It is generally acknowledged that under these circumstances the disease itself is treated in the most effective manner Secondly, a diet of sufficient caloric value should be offered the patient so that his health and strength may be maintained at a normal level It is readily appreciated that these two guiding principles of treatment are diametrically opposed to each other in many respects The one demands a restricted diet, and in many instances, undernutrition, the other calls for a larger amount of food The first aims at treating the disease, diabetes mellitus, the second attempts to conserve the nutrition of the patient The neglect of either factor may entail undesirable results

During the past years emphasis has been continually placed on the dietary restriction and the prevention of glycosuria Previously, on account of lack of full appreciation of the results which could be obtained by a more drastic curtailment of the food calories, this idea was not pushed to its logical conclusion of controlling the glycosuria of nearly every diabetic patient Through the efforts of F M Allen, by systematic and radical reductions in the food, this may be easily accomplished in most cases [1] The widespread use of these very limited diets has brought up the question of how little the individual may eat and yet remain physically and mentally fit It is the object of the present paper to furnish at least a partial answer to this question

At present it is believed that "diabetics generally have no higher food requirement than normal, and, on account of undernutrition and lessened muscular activity, will tend to maintain equilibrium on a smaller number of utilizable calories than normal persons"[2] One factor which the above statement implies is that the lower the nutri-

* Submitted for publication Nov 26, 1917
* From the Medical Clinic of the Johns Hopkins Hospital
1 Allen, F M Boston Med and Surg Jour, 1915, **172**, 241
2 Allen, F M, and Du Bois, E F The Archives Int Med, 1916 **17**, 1010.

tional state of a diabetic or anyone else becomes, the less will be the food requirements necessary to reach a maintenance level When such a subnormal state is reached, and the main object of treatment is to keep the patient alive and not necessarily efficient, a partial failure in our therapeutic aims must be acknowledged The maintenance diet, under ideal conditions, should be sufficiently high not only to enable the patient to live, but also to carry on an average amount of physical and mental work without undue fatigue

The standard for maintenance for the diabetic may be sought for in one of two criteria first, the caloric requirement, and second the nitrogen equilibrium The caloric requirement may be readily ascertained according to the height-weight formula of Du Bois and Du Bois [3] Food administered in accordance with this standard[4] should satisfy all theoretic demands The nitrogen equilibrium represents the lowest possible diet which could be exacted of any patient Food, under these circumstances, results in the conservation of the protein tissues, but does not necessarily prevent the loss of fat This principle has been applied in the treatment of obesity, it was successfully used in the prolonged dietetic experiments of Chittenden on normal people, and is employed here No living being can afford to lose muscle and glandular tissue indefinitely How far the fat store of any individual may be depleted with advantage is another question There is much to be said in favor of allowing the diabetic to become thin, so that his metabolism may be established at a lower level, as has so frequently been urged but it should be distinctly appreciated that this loss of weight should occur in the fats and not in the vitally necessary proteins It is with these ideas in mind that the nitrogen equilibrium has been chosen as the lowest possible food standard by which diabetics may be maintained in a state of physical and mental wellbeing over long periods

The kind of food provided for the diabetic may ultimately prove to be of more importance than is accredited to it at present That a protein-fat diet low in carbohydrate should be employed is common knowledge The proportion of fat and protein, however, and the height to which the protein-fat foods are raised before carbohydrates are added are still open questions which are answered in widely divergent ways by different clinicians In the present observations the diets outlined in Tables 1 and 2 were used whenever possible These are as low in fats as it is possible to make them and yet render them palatable over long periods, and they afford the maximum variety of which a carbohydrate-free list is capable The low fat content of these diets was insisted on as being the most satisfactory manner in which to

3 Du Bois, D, and Du Bois E F The Archives Int Med, 1916, **17**, 863
4 Gephart, F C, and Du Bois, E F The Archives Int Med, 1916, **17**, 902

TABLE 1—Diets of Specified Caloric Value in Which the Fat Is Kept at a Low Level The Protein and Fat Are Approximately Equal to Each Other, Gram for Gram From These Tabulations, Approximate Diets of Any Caloric Value May Be Readily Calculated These Are the Diets Used in Most of the Present Observations[5]

Food	500 Calories Gm or C c	1,000 Calories Gm or C c	1,500 Calories Gm or C c	2 000 Calories Gm or C c
Breakfast				
Eggs	(1) 50	(2) 100	(2) 100	(2) 100
Bacon*	40	50	60	
Ham				75
Butter		5	10	15
Vegetables†				100
Black coffee				
Dinner				
Broth	150	150	150	160
Steak‡	40	100	140	160
Vegetables†	200	200	200	300
Cream cheese			20	30
Butter	5	10	15	20
Olive oil		10	15	15
Black coffee				
Supper				
Broth	150	150	150	160
Eggs			(1) 50	(2) 100
Steak‡	40	75	100	140
Vegetables†	200	200	200	300
Butter	5	10	15	20
Tea (plain)				
Total Value of				
Protein	40 4	71 2	99 9	135 7
Fat	31 0	71 6	110 7	144 4
Carbohydrate	12 0	12 0	12 5	21 7
Calories	503	1,006	1 489	1 986

* The bacon is weighed uncooked The fat and protein content is calculated for the cooked product

† Two or three different vegetables should be chosen from the accompanying list (Table 2), which tabulates the vegetables containing 5 per cent or less of carbohydrates

‡ The calorie equivalent of other carbohydrate free meat or fish should be frequently substituted from the accompanying list (Table 2), to furnish variety in the diet

5 For complete details of these diets, see Jour Med Soc New Jersey 1916 **13,** 339

TABLE 2—LIST OF MEATS, FISH AND VEGETABLES ALLOWED IN THE DIETS OF TABLE 1 THE MEATS ARE TABULATED IN UNITS APPROXIMATELY THE CALORIC EQUIVALENT OF 10 GM OF BEEFSTEAK, AND MAY BE SUBSTITUTED FOR THE SAME CALORIC VALUE OF BEEFSTEAK IN TABLE 1

CALORIC EQUIVALENT OF 10 GM OF STEAK IN CARBOHYDRATE-FREE MEAT OR FISH

Food	Gm	Fat, Gm	Protein, Gm	Calories
Steak	10	1 0	2 4	19
Roast beef	5	1 4	1 1	18
Tongue	7	1 4	1 6	20
Lamb chop	5	1 5	1 1	18
Roast lamb	8	1 3	1 6	20
Sweetbreads	11	0 1	4 4	19
Boiled ham	7	1 4	1 5	19
Fried ham	6	1 7	1 1	20
Roast pork	9	0 9	2 6	19
Bacon	9	1 7	0 9	20
Chicken	11	1 0	2 4	19
Duck	9	1 3	1 8	19
Guinea hen	12	0 8	2 8	19
Squab	9	1 1	2 1	19
Turkey	7	1 3	2 0	20
Bluefish	13	0 6	3 5	20
Halibut	16	0 7	3 3	20
Mackerel	15	1 0	2 5	20
Sardines in oil	7	1 4	1 6	20

VEGETABLES ALLOWED ON "CARBOHYDRATE-FREE" DIET

Asparagus	Cucumbers	Lettuce	Spinach
Brussels sprouts	Eggplant	Pickles (sour)	String beans
Cabbage	Endive	Rhubarb	Swiss chard
Cauliflower	Greens	Sauerkraut	Tomatoes
Celery	Kohl rabi	Sorrel	Watercress

control acidosis It may be noted that the fats and proteins remain approximately equal to each other, gram for gram, throughout these diets

The nitrogen of the food was either calculated according to Atwater and Bryant's tables,[6] or actually determined by analysis The correspondence between the two methods was close enough to justify the use for the present purposes of the values as given in the tables The nitrogen of the food, urine and feces were all determined by the

6 Atwater, W O, and Bryant, A P Bull No 28, U S Dept Agric, 1906

Kjeldahl method Most of these patients were under strict supervision, either in a small metabolism ward or in the private rooms Twenty-four cases were studied Of these, only a few will be given in detail The urinary glucose was estimated by Benedict's[7] modification of Fehling's solution, the acetone substances in the urine by Shaffer's[8] procedure, and the blood sugar by the method of Lewis and Benedict[9] or that of Bang[10]

The number of calories of the protein-fat diet necessary to bring about nitrogen equilibrium was found to be slightly greater than, equal to, or considerably less than the total average caloric requirement of persons of the same age and sex as the diabetics (Tables 3 and 4)

Since it is known that "if a given subject's basal metabolism is more than 10 per cent from the average, it may be regarded as abnormal, but cannot be proved abnormal unless the departure is at least 15 per cent ,"[11] it may be concluded that the amount of food demanded to result in a nitrogen balance is not greater, in any one of the present series of cases, than the upper limits of normal metabolism, but may be lower (Table 4) This finding for diabetics is in strict accord with that of E Voit and Korkunoff,[12] who demonstrated that under normal conditions, "if fat and meat be ingested together, the quantity of the latter necessary to establish nitrogenous equilibrium is reduced to between 1 6 to 2 1, the starvation minimum "

The case[13] detailed in Table 5 demonstrates at what a low level of metabolism a nitrogen balance may be obtained This child was evidently an instance of "total diabetes " The D N ratio was constantly in the neighborhood of 3 65 1, indicating that no carbohydrate, derived either from the small amount of ingested starch or from the protein, was utilized Inasmuch as starch, whether preformed or derived from protein, has been considered the most efficient sparer of nitrogen, it is remarkable that in this patient nitrogen equilibrium could be effected on a diet of 19 calories per square meter per hour, which is only a fraction of the normal standard (Boys 12 to 13 years of age on such a diet may be considered to have normal standard of metabolism of 54 9 calories per square meter per hour, Gephart and Du Bois do not give any figures for the normal basal metabolism of girls) On calculating the metabolism for the whole period of observation it is noted that although only 0 49 gm of nitrogen were lost per day, yet the food

7 Benedict, S R Jour Am Med Assn, 1911, **57**, 1193
8 Shaffer, P A Jour Biol Chem, 1908, **5**, 211
9 Lewis, R C, and Benedict, S R Jour Biol Chem, 1915, **20**, 61
10 Bang, I Biochem Ztschr, 1913, **57**, 300
11 Gephart, F C, and Du Bois, E F The Archives Int Med, 1916, **17**, 906
12 Lusk, G Science of Nutrition, Ed 3, 1917, p 254
13 This patient was studied in the pediatric clinic under Dr J Howland, the blood sugar was determined by Harold L Higgins

TABLE 3—Condensed Data from Cases of Diabetes Mellitus, Which Show, by Periods, the Relation of the Caloric Value of the Diet to Maintenance, as Measured by the Nitrogen Equilibrium The Daily Caloric Value of the Food Was Approximately Constant During Each Period

Patient	Period, Days	Glycosuria, Gm per Day	Nitrogen per Day, Gm: Intake	Nitrogen per Day, Gm: Output, (Urine and Feces)	Nitrogen per Day, Gm: Balance	Carbohydrate Free Diet, Calories per Day*	Calories per Kilo per Day	Calories per Sq M per Hour
Case 1 Med Hist Nos 36890 and 37408 Man aged 38 Height, 5 ft 7 in (170 cm) Weight 100 lbs (45 4 kg) General condition, very poor	3	0	11 4	14 9	—4 5	1,006	22 2	27 8
	4	0	16 1	17 9	—1 8	1,503	33 1	41 6
	7	0	17 9	16 7	+1 2	1,704	37 5	47 2†
	9	Trace	22 2	21 6	+0 6	2,003	44 1	55 4
				Two	months	later		
	9	6	15 6	16 7	—1 1	1,504	33 1	41 6
	5	0	10 7	14 8	—4 1	950	20 9	26 3
	3	0	15 1	15 9	—0 8	1,473	32 4	40 8
	14	0	18 5	17 6	+0 9	1,711	37 7	47 4
	16	0	18 9	17 7	+1 2	1,984	43 7	54 9
Case 2 Med Hist No 36901 Woman, aged 35 Height, 5 ft 6 in (168 cm) Weight, 111 lbs (50 4 kg) General condition, fair	4	45	17 6	16 1	+1 5	1,487	29 5	39 7
	2	30	18 4	17 5	+0 9	1,811	35 9	48 4
	4	8	13 7	14 6	—0 9	1,106	21 9	29 5
	3	0	4 6	9 0	—4 4	591	11 7	15 6
	2	0	14 5	15 8	—1 3	1,182	23 5	31 6
	5	0	20 0	14 4	+5 6	1,750	34 7	46 7
Case 3 Med Hist No 37161 Man, aged 43 Height, 5 ft 10 in (178 cm) Weight 110 lbs (49 9 kg) General condition, poor	8	0	14 0	15 2	—1 2	1,412	28 3	36 3
	3	0	11 4	15 5	—4 1	988	19 8	25 4
	3	0	18 5	15 2	+3 3	1,700	34 1	43 7
	6	0	19 4	17 9	+1 5	2,104	42 2	54 1
	1	0	7 4	13 8	—6 4	500	10 0	12 9
	2	0	25 6	18 2	+7 4	2,193	44 0	56 4
Case 4 Med Hist No 36776 Woman, aged 56 Height, 5 ft 3½ in (161 cm) Weight 132 lbs (59 9 kg) General condition, normal	7	3	7 9	11 5‡	—3 6	712	11 9	18 2
	4	0	13 1	12 9‡	+0 2	1,133	18 9	29 0
	3	0	1 6	5 5‡	—3 9	49	0 8	1 3
	2	0	11 6	11 4‡	+0 2	1,056	17 6	27 0
	11	0	15 1	11 9‡	+3 2	1,523	25 4	39 0
Case 5 Med Hist No 37488 Man, aged 26 Height 5 ft 9 in (175 cm) Weight, 128 lbs (58 1 kg) General condition, fair	7	0	14 7	12 9	+1 6	1,470	25 3	35 9
	3	0	20 0	14 1	+5 9	1,943	33 4	47 4

* "Carbohydrate free" diets contain approximately the proportion of proteins, fats and carbohydrates given in Table 1, with the exception of Cases 8 and 9, in which the carbohydrate content of the food was somewhat higher

TABLE 3—CONDENSED DATA FROM CASES OF DIABETES MELLITUS, WHICH SHOW, BY PERIODS, THE RELATION OF THE CALORIC VALUE OF THE DIET TO MAINTENANCE, AS MEASURED BY THE NITROGEN EQUILIBRIUM THE DAILY CALORIC VALUE OF THE FOOD WAS APPROXIMATELY CONSTANT DURING EACH PERIOD—*Continued*

Patient	Period, Days	Glycosuria, Gm per Day	Nitrogen per Day, Gm Intake	Output, (Urine and Feces)	Balance	Carbohydrate Free Diet, Calories per Day*	Calories per Kilo per Day	Calories per Sq M per Hour
	4	45	12 6	15 5	—2 9	1,318	21 2	33 8
Case 6 Med Hist No 37267 Man, aged 35	3	22	10 2	14 7	—4 5	988	18 2	25 3
Height, 5 ft 7 in (170 cm)	5	0	5 4	10 9	—5 5	421	7 8	10 8
Weight 120 lbs (54 4 kg)	**4**	**0**	**13 3**	**12 0**	**+1 3**	**1,099**	**20 2**	**28 2**
General condition, normal	**4**	**0**	**15 9**	**13 6**	**+2 3**	**1,465**	**26 9**	**37 5**
	8	**0**	**18 0**	**15 5**	**+2 5**	**1,728**	**31 9**	**44 3**
Case 7 Med Hist No 37261	6	5	15 6	23 0	—8 0	1,503	24 4	36 1
Man, aged 41 Height, 5 ft 8 in	5	0	15 6	17 3	—1 7	1,505	24 4	36 1
(173 cm) Weight, 136 lbs	3	0	17 0	17 1	—0 1	1,614	26 2	38 7
(61 7 kg) General condition,	3	0	18 8	23 1	—4 3	1,903	30 8	45 6
normal	**3**	**0**	**21 4**	**19 9**	**+1 5**	**2,048**	**33 2**	**49 1**
	12	0	8 2	9 9	—1 7	609	17 9	20 9
	3	**0**	**13 4**	**10 8**	**+2 6**	**1,152**	**33 9**	**39 5**
	2	Trace	12 6	16 9‡	—4 3	1,284	37 8	44 0
Case 8 Med Hist Nos	5	0	7 4	10 0‡	—3 5	595	17 5	20 4
36887 and 37230 Boy, aged 13	9	0	13 5	14 6	—1 1	1,157	34 0	39 6
Height, 4 ft 11 in (150 cm)	6	0	14 9	15 3	—0 4	1,449	42 6	49 7
Weight 75 lbs	5	0	15 4	15 7	—0 3	1,363	40 1	46 7
(34 0 kg) General condition,				Six	weeks	later		
normal	3	0	12 9	15 2	—2 3	1,101	32 4	37 7
	6	**0**	**18 4**	**16 4**	**+2 0**	**1,508**	**44 4**	**51 7**
	1	0	8 4	9 4	—1 0	620	18 2	21 2
	7	**0**	**21 7**	**19 0**	**+2 7**	**1,686**	**49 6**	**57 8**
	1	0	5 9	13 4	—7 5	532	19 6	19 5
	8	0	8 5	9 9	—1 4	994	36 5	36 4
Case 9 Med Hist No 36838	7	0	7 0	8 0	—1 0	570	21 0	20 9
Girl, aged 12 Height, 5 ft 1½ in	11	Trace	8 7	9 9	—1 2	858	31 5	31 4
(156 cm) Weight, 60 lbs	4	0	5 8	8 5	—2 7	529	19 5	19 4
(27 2 kg) General condition,	8	0	8 6	8 8	—0 2	840	30 9	30 8
poor	2	0	4 6	9 5	—4 9	360	13 2	13 2
	11	0	8 6	9 9	—1 3	832	30 6	30 5

† The figures printed in heavy type indicate periods in which a positive nitrogen balance was obtained, the figures in lighter print indicate the periods of nitrogen loss

‡ In these instances, the nitrogen of the feces was estimated as 10 per cent of the nitrogen intake, the remaining figures represent actual determinations

TABLE 4—Summary of Table 3 Caloric Requirement Necessary to Produce Nitrogen Equilibrium in Cases of Diabetes Mellitus, as Compared with the Normal Metabolism of Individuals of the Same Age and Sex

Case	Age	Sex	General Condition	Calories per Hour per Square Meter of Body Surface: Highest at which N Equilibrium Was Not Obtained	Lowest at which N Equilibrium Was Obtained	Normal Metabolism*	Caloric Requirements Necessary to Establish N Equilibrium as Compared with Normal Metabolism
1, Period 1	38	M	Very poor	41 6	47 2	43 7	8 per cent higher
Period 2				41 6	47 4	43 7	8 per cent higher
2	35	F	Fair	31 6	39 7	40 6	Unchanged
3	43	M	Poor	36 3	43 7	43 7	Unchanged
4	56	F	Normal	18 2	27 0	36 0	25 per cent lower
5	26	M	Fair		35 9	43 7	18 per cent lower
6	35	M	Normal	33 8	28 2	43 7	28 per cent lower
7	41	M	Normal	45 6	49 1	43 7	12 per cent higher
8, Period 1	13	M	Normal	49 7	39 5	54 9	28 per cent lower
Period 2				37 7	51 7	54 9	6 per cent lower
9	12	F	Poor	36 4			

* Basal metabolism according to F C Gephart and E F Du Bois (The Archives Int Med, 1916, 17, 902) plus 10 per cent to allow for the specific dynamic action of the diet

actually utilized amounted to only 13 9 calories per kg per day, or 12 9 calories per square meter per hour This remarkable effect of a low, pure protein-fat diet in conserving the body's nitrogen may be the reason for the fact that this emaciated child was able to "walk around and go riding" three months later, although she was still excreting large amounts of sugar The present case is one of the rare instances in which a maximal D N ratio did not prove to be a sign of immediate danger or impending death The fluctuations manifested in the D N ratio from day to day are similar to those noted in other cases, and may be explained by irregular periods of glucose excretion and retention and not necessarily through inefficiency in the management of the case [14]

From the clinical point of view it is extremely important to know whether or not it is possible to restore the lost body tissue, in other words, cause an assimilation of nitrogen, on these diets The generally accepted fact is that it is difficult to cause a prolonged deposition of protein on a protein-fat diet [15] Strictly speaking, the "carbohydrate-free" diets used in diabetes, as in the present report, contain from 10

14 Mosenthal, H O, and Lewis, D S Bull Johns Hopkins Hosp, 1917, 28, 187

15 Lusk, G Science of Nutrition, Ed 3, 1917, p 255

TABLE 5.—DATA FROM A CASE OF DIABETES MELLITUS, GIRL, AGED 8 YEARS, 9 MONTHS, HEIGHT, 4 FEET 8 INCHES (142 CM.), WEIGHT, 47 POUNDS 3 OUNCES (21.4 KG.). THIS PATIENT IS SUFFERING FROM SEVERE DIABETES MELLITUS, AS SHOWN BY THE VERY HIGH D : N RATIO, AT THE SAME TIME HER CALORIC REQUIREMENTS NECESSARY TO ESTABLISH NITROGEN EQUILIBRIUM ARE VERY LOW

Date	Urine					Blood Sugar, per Cent	Food						Nitrogen Balance, Gm.*	Calories Utilized†		
	Glucose, Gm.	Acetone Bodies as B. Oxy., Gm.	N, Gm.	D : N Ratio	Calories Lost as Glucose and B. Oxy.		Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Alcohol, Gm.	Total Calories	Nitrogen, Gm.		Total	Per Kg.	Per Sq. M. per Hour
6/20/16	75.6				280	0.49										
6/21/16	36.0	14.7	4.70	6.0	199	0.25	15.2	1.2	7.5		101	2.43	—2.51	0	0.0	0.0
6/22/16	41.6	19.7	8.61	2.9	213	0.25	28.3	2.1	16.5	5.5	212	4.53	—4.56	0	0.0	0.0
6/23/16	37.8	14.9	6.94	2.8	207	0.33	31.1	2.3	18.0	5.5	261	4.98	—2.46	51	2.5	2.3
6/24/16	17.8	7.9	6.50	2.7	102		44.0	4.0	0.0	5.5	256	7.04	—0.16	154	7.2	6.7
6/25/16	37.4	7.5	10.72	2.1	172		81.4	20.4	14.1	5.5	620	13.02	+1.00	448	20.9	19.5
6/26/16	26.8	5.8	7.82	1.0	105		70.0	28.2	19.1	5.5	666	11.20	+2.26	561	26.2	24.4
6/27/16	+5.8‡	+4.2‡	+3.71‡	1.5	+41‡	0.33	13.2	1.2	0.0	5.5	104	2.11		0	0.0	0.0
6/28/16	47.4	7.7	8.51	3.6	210	0.31	48.5	15.4	19.1	5.5	316	7.76	—1.53	106	4.9	4.6
6/29/16	47.7	8.8	9.22	3.1	216		48.5	15.4	19.1	5.5	316	7.76	—2.24	100	4.6	4.3
6/30/16	17.7	6.7	5.11	3.4	96	0.27	13.2	1.2	0.0	5.5	104	2.11	—3.21	8	0.3	0.4
7/ 1/16	23.0	7.2	6.30	3.7	117		15.4	1.4	0.0	5.5	115	2.46	—4.09	0	0.0	0.0
7/ 2/16	52.9	5.7	8.13	4.1	221		65.1	29.7	19.1	5.5	660	10.42	+1.25	439	20.5	19.1
7/ 3/16	55.0	9.1	9.94	3.5	244		73.4	28.9	18.0	5.5	682	11.74	+0.63	438	20.4	19.0
7/ 4/16	64.5	13.1	10.53	4.4	298		93.9	43.8	18.0	5.5	905	15.02	+2.99	607	28.3	26.4
7/ 5/16	52.8	11.2	8.93	3.9	246		97.9	28.1	18.0	5.5	775	15.66	+5.16	529	24.7	23.0
7/ 6/16	54.2	11.5	16.55	2.1	252		90.5	46.3	18.0	5.5	914	14.48	—3.52	662	30.9	28.7
7/ 7/16	61.4	13.2	11.78	3.6	287	0.32	103.6	55.1	18.0	5.5	1,049	16.58	+3.14	762	35.6	33.1

* Ten per cent. of the nitrogen of the food is calculated as being excreted in the feces.
† The figures of these columns represent the total number of food calories, less the calories lost in the urine as glucose and Beta oxybutyric acid.
‡ Urinary specimen incomplete on this day.

Summary: From June 20 to July 6, inclusive, excepting June 27

Total food calories	7,985	Calories utilized per kilo per day	13.9
Total calories lost in urine	3,215	Calories utilized per square meter per hour	12.9
Total calories utilized	4,770	Total nitrogen lost, gm.	7.85
Calories utilized per day	298	Nitrogen lost per day, gm.	0.49

to 15 gm of starch derived from the vegetables It is rather problematical what effect such a small amount of carbohydrate may have In some instances, there is no tendency for the body to assimilate nitrogen to any marked degree This is exemplified in Case 1, Table 3 This patient showed no appreciable rise in his slight positive nitrogen balance when the diet was increased after nitrogen equilibrium had once been obtained, either in the first or second periods of study On the other hand, some diabetics exhibit the ability to assimilate nitrogen while on "carbohydrate-free" diets This may be noted in Table 3, Case 2 retained 28 gm of nitrogen in 5 days, Case 4, 35 gm in 11 days, Case 5, 29 gm in 10 days, Case 6, 34 gm in 16 days, and one diabetic patient of this series whose protocol is not charted, retained 49 gm of nitrogen in 17 days It is perfectly apparent from these data that the diabetic may often build up body protein while on a carbohydrate-free diet

A study of Tables 3 and 4 reveals some apparent contradictions In Cases 6 and 8, the highest caloric value of the food at which nitrogen equilibrium was not obtained is greater than the lowest value at which equilibrium was obtained These inconsistent results are no more opposed to one another than the very varying heights of metabolism required to produce nitrogen equilibrium in the different cases (Table 4) What the specific reason for the caloric requirement is in each case is impossible to determine, it may be stated definitely, however, from the data of Case 1 (Tables 3 and 4), that these factors may have a tendency to remain constant, although in some individuals they may vary as in Cases 6 and 8

In Case 6, Table 3, it is apparent that in the first two periods the nitrogen output is higher, with a lower nitrogen intake than it is in some of the subsequent periods The same fact may be noted in Case 2, Table 3 In both of these patients there was a considerable glycosuria, while this slight excess of urinary nitrogen manifested itself It may have been that the caloric loss of the urinary sugar resulted in a greater destruction of protein, or it may be that these are mild examples of the very marked protein breakdown and excessive amounts of urinary nitrogen at times found in diabetes, as in the case of Geyelin and Du Bois[16] In either event it is certain that nitrogen equilibrium was established at a considerably lower caloric food level in Case 6 after the glycosuria had subsided It must be distinctly recognized, however, that the glycosuria in itself, although very marked, need not result in an increased caloric demand to establish nitrogen equilibrium This is well shown in the case detailed in Table 5

The discrepancy in Case 8 is well explained in Table 6, which gives

16 Geyelin, H R, and Du Bois, E F Jour Am Med Assn, 1916, **66**, 1532

TABLE 6—An Abstract from the Complete Protocol of Case 8, Table 3 Effect of a Slight "Cold" on Glycosuria Acetonuria, Blood Sugar and Nitrogen Equilibrium in a Case of Diabetes Mellitus, Boy, Aged 13

Date	Urine					Feces Nitrogen, Gm	Output Nitrogen, Gm	Balance Nitrogen, Gm	Food						Blood Sugar, per Cent	Remarks
	Volume C c	Glucose	Acetone	Diacetic Acid	Nitrogen, Gm				Nitrogen, Gm	Protein, Gm	Fat, Gm	Carbohydrate, Gm	Total, Calories	Calories per Sq M per Hour		
11/16/16	1,245	0	++	+	10.08	0.60	10.68	+0.15	10.83	67.7	51.3	31.3	911	31.2	0.10	
11/17/16	1,070	0	+	+	8.67	0.60	9.27	+3.74	13.01	81.3	66.6	44.2	1,134	38.9		
11/18/16	1,670	0	+	+	11.86	0.60	12.46	+0.55	13.01	81.3	66.6	44.2	1,134	38.9		
11/19/16	1,260	0	++	+	9.95	0.60	10.55	+3.50	14.05	87.8	69.6	44.2	1,188	40.7		Contracted slight "cold"
11/20/16	1,605	Trace	+++	++	14.28	0.60	14.88	—0.82	14.06	87.9	85.5	44.2	1,337	45.8	0.13	
11/21/16	1,640	Trace	++	+	13.04	0.80*	18.84	—7.62	11.22	70.1	82.2	13.9	1,232	42.2		
11/22/16	1,260	0	++	+	7.28	0.80*	8.08	—5.47	2.61	16.5	0.9	18.0	150	5.1		
11/23/16	990	0	++	+	9.41	0.80*	10.21	—3.43	6.78	42.4	31.0	18.1	536	18.3		Maximal temperature, 99.8 F, temperature normal on all other days
11/24/16	1,435	0	++	+	11.05	0.80*	11.85	—5.26	6.59	41.2	33.6	18.0	555	19.0		
11/25/16	1,870	0	++	+	10.29	0.80*	11.09	—2.00	9.09	56.8	52.8	18.0	798	27.3		
11/26/16	2,620	0	++	+	12.31	0.91	13.22	—1.54	11.68	73.0	60.6	18.0	937	32.1		
11/27/16	2,680	0	++	+	13.40	0.91	14.31	—2.13	12.18	76.1	66.3	18.0	1,002	34.3		
11/28/16	1,840	0	+	+	10.12	0.91	11.03	—1.71	12.74	79.6	66.6	18.0	1,020	35.0		
11/29/16	2,550	0	+	0	13.77	0.91	14.68	—0.54	14.14	88.1	64.6	20.3	1,047	35.9		
11/30/16	2,030	0	+	0	13.40	0.91	14.31	—1.61	12.70	79.4	80.9	18.0	1,152	39.5		
12/ 1/16	2,360	0	++	0	13.92	0.91	14.83	—0.09	14.74	92.1	77.5	33.3	1,235	42.3	0.09	
12/ 2/16	2,300	0	++	0	13.34	0.91	14.25	—0.94	13.31	83.2	83.8	31.3	1,249	42.8		

* Nitrogen content of feces estimated, not determined

a portion of the protocol in detail In the first days a nitrogen balance was readily obtained on a diet of about 1,000 calories On November 19 a definite series of changes appeared Each one of these variations in itself might not have been worthy of attention, but taking them together they showed that many of the metabolic processes were synchronously affected The acetone and diacetic acids increased in the urine, as shown by the qualitative tests, a trace of glucose was found in the urine, the nitrogen excretion rose considerably, the nitrogen balance became negative, and the blood sugar increased, although the diet was scarcely changed for three days All of these phenomena were evidently brought about by a "cold in the head" of so slight a nature that the patient himself scarcely complained of it, and the body temperature only rose to 99 8 F on one day All these symptoms promptly rectified themselves with the disappearance of this infection of minimal intensity, except one the power to establish nitrogen equilibrium at the former low diet level was lost and remained so when the patient was tested out again six weeks later It is well known that nervous shocks and the severer infections play havoc with the health of diabetics That a very slight disturbance should have such far-reaching effects is worthy of consideration in the management of these cases

A study of Tables 3, 4 and 5 shows that the general condition of the diabetic, that is, whether his state of nourishment be normal, fair, poor or emaciated, tends to have no direct bearing on the number of calories per square meter per hour required to establish nitrogen equilibrium

Case 9 (Tables 3 and 4) is an instance of a patient in whom nitrogen equilibrium could not be established without the appearance of glucose in the urine The treatment in this case was to continue the inadequate diet and maintain the urine in a sugar-free condition The result has been a slow but evidently perceptible loss of weight and strength Case 4 (Tables 3 and 4), a woman in good circumstances, has continued on the given diet for one year, attending to her social and household duties, and has gained strength and a little weight, although her diet is a low one In Case 5 (Tables 3 and 4), the patient has taken the low diet indicated for an interval of 6 months, during this period he has solicited contracts for an engineering company, being on his feet nearly all the time, and feels perfectly strong and well In Case 7 (Tables 3 and 4) the patient reports that he has taken the 2,000-calory carbohydrate-free diet for a period of eight months while he has been working as a farmer, and that his health and strength are good, though he has gained no weight These few examples may serve to indicate (they are too few to prove the claim) that a diabetic need take only sufficient calories to result in a nitrogen equilibrium in order to bring about a maintenance of health and strength

CONCLUSIONS

Diabetic patients may be established in nitrogen equilibrium by a carbohydrate-free diet having a caloric value equal to the standard total caloric requirement. In many instances this may be accomplished at a considerably lower level of feeding. The factors which determine the dietary level at which a diabetic attains a nitrogen balance are apparently very numerous, and not fully determined; glycosuria at times, and infections, even of very slight degree, may necessitate a higher diet to bring about the desired result.

A marked assimilation of nitrogen may occur in diabetics while on a carbohydrate-free diet.

The lowest diet which will conserve the physical and mental efficiency of the diabetic is that which maintains the nitrogen equilibrium of the patient. A rough estimate for clinical purposes of what constitutes a maintenance ration for the diabetic on a carbohydrate-free diet, is from 1,500 to 2,000 calories. In adjusting the value of the diet it should be borne in mind that women and small persons generally require less food than men and larger persons.

THE DISTRIBUTION OF BILE IN CERTAIN TYPES OF JAUNDICE*

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CLEVELAND

In a previous publication from this clinic[1] it was proposed by me to examine the blood for bile in cases of jaundice, and a scheme devised to make measurements on blood, stool and urine which, when correlated with the color of the skin, might throw some light on the rôle of bile in the various types of jaundice The work covered by this report is the examination of 395 specimens of blood plasma together with an examination of the urine and skin, and in a lesser number an examination of stool and duodenal contents, according to that scheme The methods employed are essentially those previously described, but with the following modifications A tintometer constructed in the laboratory is now used to measure the color of the plasma, and readings can be made more accurately than by our earlier method, by which test tubes were simply held parallel and observed down the length of the tube The color of the plasma is taken as an index of the bilirubin content and the amount is expressed by a number corresponding to the number of times the plasma must be diluted to reduce the color to a tint that can just be discerned in a column 1 cm deep

I am of the same opinion as formerly expressed, that the yellow color of plasma is due solely to bilirubin, and that Gmelin's test with nitric acid can be used to test for it To substantiate this claim I made parallel tests in 239 cases, using Gmelin's and the Huppert-Cole tests The results were identical in 224 cases, contradicting in 15 In 3, the Huppert-Cole was positive while the nitric acid test was negative In 12 the nitric acid test was positive and the Huppert-Cole test negative But the value of the Huppert-Cole tests depends to a certain extent on the quantity of plasma used, and it is sometimes negative because not enough plasma is available This slight discrepancy is certainly explainable by the difference in delicacy of the tests and does not disprove at all the identity of the substance tested for

The test for bile salts in the blood is modified so that we may now dialyze 3 c c of plasma in 9 c c of water through collodion sacs, where

* Submitted for publication Nov 18, 1917
* Read before the Association of American Physicians, May, 1917

1 Blankenhorn, M A The Bile Content of the Blood in Pernicious Anemia, The Archives Int Med, 1917, **19**, 344

formerly we dialyzed 5 c c into 10 c c of water and alcohol For cholesterol in the blood I have found no satisfactory and practicable method

Bile Pigment—Three hundred and ninety-five specimens of blood plasma were examined in this manner Of this number, seventy-five were described as colorless, that is, there was no distinct yellow color present, there being only a faint turbidity, or a faint pink or buff tint distinguishing the specimen from water This group of seventy-five all gave negative results when tested chemically for bilirubin

Two hundred and twenty-two specimens were distinctly yellow and gave a chemical test for bilirubin The specimens of this group measured from 15 to 375 Forty represents the critical point at which the cholemia becomes a visible jaundice Of the 222 specimens, only two were over 40 without the patient being jaundiced, and but ten were under 40 with the patient jaundiced

Between the 75 specimens and the 222 giving a chemical test for bilirubin were 94 specimens that were distinctly yellow in color, but gave no chemical test for bilirubin It is in this group that the possibility of the presence of some yellow substance other than bilirubin must be seriously considered In this group was the blood from 10 primary anemia patients, from 7 patients who had been jaundiced previously, from 11 with acute infectious diseases in which jaundice is very common, and 6 with some disease of the liver or gall ducts, that is, 34, or about one third, in which bilirubin is commonly found In some of them bilirubin had actually been found previously, and in others it was found subsequently Inferentially, we can say that bilirubin was present in one third of all these, but in amounts too small to be detected chemically The remaining two thirds were all from normal individuals or patients admitted to the hospital for some condition not associated with jaundice In all this class of doubtful, subicteric plasmas, at no time was there ever present any pigment in large amounts I have repeatedly tested those specimens for luetin and urobilin, which are supposed to pigment the plasma at times, but in this group neither of these was found And since it is common to find bilirubin in amounts large enough to be tested chemically in perfectly normal persons, it is safe to assume that bilirubin is the pigment in this entire group of 94

By an analysis of the 222 specimens of blood plasma that contained bilirubin in amounts large enough to give a chemical test, considerable light is thrown on the behavior of bilirubin, per se This has aided distinctly in the interpretation of the various findings in particular groups of cases and somewhat in the interpretation of individual cases As indicated in the foregoing, the degree of staining of the plasma

varied from 15 to 375 and 40 represents the critical point at which the cholemia becomes jaundice, 100 represents a distinct jaundice, 300 and over a marked jaundice The series does not contain a case of that very extreme jaundice sometimes seen in prolonged, complete biliary obstruction

One hundred and forty-one of the specimens were from jaundiced patients, 81 were from patients not jaundiced In the group of 81 are 14 from normal patients, 20 from patients admitted for conditions in no way associated with jaundice I frequently find blood plasma very distinctly stained with bilirubin where there is absolutely no explanation, unless it be that a relative degree of cholemia is normal A goodly number of these cases were investigated repeatedly and the findings confirmed, but no individual or physiologic variation can be described as yet On the other hand, the degree of cholemia was frequently found distinctly above 40, the critical point where jaundice should be expected, yet none could be observed by the ward physicians Three were found at 50 or over

Of the 395 examinations made, it was found in seven cases that the patient was described as jaundiced, but the plasma was found absolutely colorless This at first suggests jaundice without cholemia, but six out of seven cases were patients with a very severe secondary anemia, in which the normal pigmentation is exaggerated by pallor and the condition simulates jaundice, the remaining one was described as doubtful We thus dismiss from this report jaundice without demonstrable cholemia

I have found that a distinctly higher degree of cholemia can exist without choluria, and 60 is found to express the critical point for choluria or the average above which cholemia becomes choluria There is, however, a wide range in the degree of cholemia without choluria, so much so that when some of the more certain factors concerned in the behavior of bilirubin in the blood are determined, this disparity may be of much diagnostic importance

One hundred and fifty-three of 220 specimens showed a chemical test for bilirubin in the plasma without choluria These ranged from 15 to 275 In many cases this retention of bilirubin was associated with impaired kidney function In other cases no other retention could be demonstrated and there was no reason to expect any impairment of kidney function The duration of the jaundice, as well as the intensity, seems to be a factor in determining this disparity In general, a more prolonged and a more severe jaundice is associated with a high cholemia when there may be no choluria Also, when there is disease of the liver with change in its size and consistency, this disparity is frequently marked In diseases of the bile ducts the disparity is less

frequent and less marked Choluria without cholemia was not seen, also choluria without jaundice, in so far as bilirubin alone is concerned, has not been observed

From the foregoing analysis of 222 cases in which bilirubin was found chemically, I am impressed with the following points in the behavior of bilirubin in the blood, that bilirubin is very commonly present in the blood of normal individuals in varying amounts, that it is usually readily diffused through the lymph into the skin, but less readily through the kidney, that it may be fixed in the blood, and thus withheld from lymph and urine, that it is not formed or retained in the lymph in higher concentration than in the blood, that it never appears in the urine without reaching and maintaining a certain concentration in the blood

Bile Salts—In studying the bile salts in the blood I have thus far found no satisfactory quantitative method Further studies on the dialysis of blood plasma through collodion into water confirms the belief that cholesterin and lecithin are not so dialyzed, and that the Pettenkofer test on the dialysate, together with the spectrum, is a specific test for bile salts It is not yet possible to bring much order out of the chaotic findings that appear in investigating bile salts, and until a quantitative method is used and a more satisfactory method is found for the urine, very little can be said with assurance about the behavior of bile salts in the blood A brief analysis of some of the results alone is justifiable

Out of 395 specimens examined, bile salts were found in 124 In 87 cases bile salts occurred in the blood in conjunction with bilirubin This occurs most commonly when bilirubin is highly concentrated in the blood and when both bile salts and bilirubin are present in the urine In 37 cases bile salts occurred alone This was most often in cases of primary anemia, acute infectious diseases, diseases of the liver in which there is change in the size and consistency of the liver, and in nephritis In 10 cases bile salts were found in conditions never associated with jaundice In 4 cases bile salts were found in normal individuals When larger amounts of plasma are dialyzed, bile salts are very often found in normal blood, and it is my impression that if 15 c c of plasma are dialyzed by the method described and all the dialysate be concentrated into 2 c c, the Pettenkofer test will be uniformly positive in normal persons In 106 cases bile salts were found in the blood, and not in the urine, in 13 bile salts were in the urine and not in the blood This disparity of salts between cholemia and choluria, with a very small number showing salts in the urine and none in the blood, but a large number with salts in the blood and none in the urine, suggests a process of retention, whether this is due to a

fixation in the blood or a diminished permeability of the kidney is not yet clear More accurate methods for examining the urine and a quantitative study of the blood are necessary to clear this up

Urobilin—One hundred and thirty-three specimens of blood were examined for urobilin and twenty-two found positive This rather large number was at first surprising after the consistently negative results which I have previously reported and which other observers report The method used is the same as that used previously, namely, the plasma is centrifuged with an equal volume of 90 per cent alcohol saturated with zinc acetate and Ehrlich's aldehyd reagent added to the clear liquid Both the purple red color and the spectrum were found in every positive test The positive results are attributed to the selection of the patients and the time of taking the specimens

Of the twenty-two positive cases, in eighteen urobilin occurred in conjunction with bilirubin, and in nine cases it was found where no jaundice was observed In three instances urobilin was found in large amounts in the plasma of patients that were not jaundiced and moreover the plasma itself was practically colorless

The urine was examined in 325 cases and urobilin found 110 times In eighty-eight cases there was urobilin in the urine with none in the blood In no instance was there urobilin in the blood, with none in the urine In but two of the patients in whom a urobilinemia was found was there any distinct impairment of the kidney In every case in which there was urobilinemia, enormous amounts were also found in the urine It is, therefore, quite obvious that there is no retention of urobilin in the blood Urobilin dialyzes very promptly into water through collodion membranes and leaves a perfectly clear and colorless dialysate, it can then be found in the dialysate by the Ehrlich aldehyd reagent and the spectroscope From the foregoing observation we can say that urobilin is frequently found in the blood in large amounts without causing jaundice, that it is very promptly yielded to the kidney, and that it does not occur in the blood unless it is formed in excessive amounts

We have over a thousand quantitative estimates of urobilin in stool and urine according to the methods of Wilbur and Addis,[2] but I do not feel that this has contributed anything to the general information on the distribution or behavior of bile The difficulties due to irregularities in the formation and elimination of stool, catharsis, etc, have not yet been overcome, otherwise the method is entirely successful

In the examination of the urine the methods used are the same as previously reported No extensive use has been made of the quanti-

2 Wilbur and Addis The Archives Int Med, 1914, **13**, 235

tative method for bilirubin, as described by Whipple[3] Although it has worked quite satisfactorily in deeply pigmented plasmas and urines, when smaller amounts of pigment are present I have difficulty in getting readable colors

In a previous publication by Hoover and myself,[4] dissociated jaundice was elaborated and some of its terms defined In the present report little can be added to the general premises of that work, especially anything on the significance of dissociation itself In considering the various groups of cases separately the dissociation begins to take some form and meaning Practically every case of jaundice, if the urine and blood be followed carefully through the onset and disappearance of the jaundice, will present dissociation at some time or other

Laennec's Cirrhosis—I have observed 18 cases of Laennec's cirrhosis with alteration in size and consistency of the liver, chiefly the small contracted liver Some of the patients had ascites Thirty-seven observations were made, bilirubinemia was found in 31 instances, and in all the 31 cases there was jaundice The bilirubinemia varied from 20 to 350 Bilirubin was found in the urine of 17 patients, but there was a marked disparity between cholemia and choluria, six plasmas were found at 60 or over without choluria, bilirubin was not withheld from the lymph, but was not always freely yielded to the kidney In none of these cases was there any great impairment of kidney function, so the bilirubin is probably fixed to the plasma In the cases in which the jaundice had been the most prolonged this fixation was most marked, the severity of the systemic symptoms was never an index to the fixation Bile salts were found in the blood in 10 cases, in the urine in 12 There seems to be no retention of the salts in the blood

There is in this group a very common and mystifying dissociation of the biliary elements in both blood and urine, from which the observer has gathered nothing but confusion In two cases there was at one time a marked increase in the bile output found in the stool, associated with a marked jaundice and deep choluria, showing that the formation of bile pigment had been increased In three cases there was a vary marked diminution of the output of bile in the stool simultaneously with a want of bile in the urine and a very moderate jaundice, showing a definite diminution of the formation of bile In five there was a distinct diminution of bile in the stool at a time when the blood, urine and skin were deeply stained, thus showing that obstruction to the drainage of bile sometimes occurs Several cases

3 Hooper and Whipple Am Jour Physiol, 1916, **40,** 332

4 Hoover, C F, and Blankenhorn, M A Dissociated Jaundice, The Archives Int Med, 1916, **18,** 289

went through a period of jaundice and ascites without showing any demonstrable change in the daily output of bile in the stool

Hanot's Cirrhosis—Three cases of Hanot's cirrhosis were examined, but very little disturbance in the formation or distribution of bile could be found, a thing quite surprising considering the alteration in the size and consistency of the liver and the general symptoms The same can be said of three cases of syphilitic disease of the liver, except of one in which there was great deformity about the hilus of the liver, as shown at necropsy, with obstruction of the ducts

Obstructive Jaundice—Nineteen cases of obstruction of the bile ducts were observed and twenty-three specimens of blood taken Twenty-three specimens contained bilirubin, most of them over 100 All were jaundiced, and all except two were accompanied by bilirubin in the urine In this group there is very little disparity between cholemia and choluria, but inasmuch as there is a higher average cholemia than in the cirrhosis group, that point in difference is of little value In twelve out of twenty-three plasmas, bile salts also were found In the urine, too, bile salts and bilirubin were very seldom dissociated in this group This consistency between bile pigment and bile salts in both blood and urine in obstructive jaundice, especially at the onset, or while the process is progressing, is regarded by me as characteristic of obstructive lesions Very few exceptions to this have been found that cannot be explained by some complication, such as septicemia, nephritis, etc After the obstruction is relieved the bile salts disappear from the urine and blood first, and we then have, of course, a dissociation, but the dissociation is of renal origin The early obstructive lesions are the best and most common examples of the so-called "complete icterus" that is, bilirubin and bile salts in both urine and blood The stool in obstructive jaundice varies in its bile content according to the extent and duration of the obstruction That the bilirubin content of the blood and urine must necessarily become greater as the amount in the stool diminishes is not true I observed three cases in which the stools were acholic for over a week, during which time the jaundice remained the same, and the same amount of bilirubin was given off each day by the urine, apparently the formation of bile had been diminished by the obstruction to an amount that could be eliminated by the kidney as fast as it was formed In all three cases there was no way of estimating the condition of the portal blood flow, so that it is not certain that biliary obstruction alone was the inhibiting factor

One case has been observed, including a necropsy, in which no lesion save obstruction could be found, yet the patient went six days with only a very slight increase in the cholemia and jaundice I am

of the opinion that under some circumstances obstruction alone will inhibit the formation of bile

Sixteen cases were investigated in which a diagnosis of cholelithiasis was made, but in which no obstruction could be proved Seven of the plasmas contained bilirubin and three bile salts, and that only in very small amounts None of the patients was jaundiced and none had bile in the urine (either pigment or salts) Seven of these patients were operated on, and in three gallstones were found, but of the three only one showed cholemia before the operation, while of the four who had no gallstones at operation, three had shown cholemia before the operation The examination of the blood for small amounts of bile has thus far been of no aid in the diagnosis of gallstones that are producing no obstruction

Catarrhal Jaundice—Seven cases of catarrhal jaundice were examined and nine specimens of blood taken Bilirubin was found in all, bile salts in four The distribution and behavior of the bile resembled obstructive jaundice in this respect there was little dissociation of the pigments and salts in both blood and urine except after the process began to subside There was also an intestinal hypocholia Unlike most obstructive lesions, there was frequently urobilin in the urine

Chronic Passive Congestion—Twelve cases of heart disease with chronic passive congestion of the liver were examined, most of them while decompensated Bilirubin was present in ten cases, bile salts in three Only small amounts of bilirubin were found, and but two of the patients were jaundiced, and only one had bile in the urine There was considerable dissociation in the blood Like Hanot's cirrhosis, there is little change in the distribution of the bile pigment in proportion to liver changes

Septicemia—Thirteen patients with septicemia were investigated, including 3 cases of typhoid, 5 of streptococcus and 4 of colon infections In 10 there was bilirubin in the plasma and 5 bile salts, 6 had large amounts and were deeply jaundiced, but only 2 of the 6 had bile salts in the blood On account of the liability to so many complications, especially nephritic, it is impossible to generalize in this small group

Pneumonia—Forty cases of pneumonia were investigated and 48 specimens examined Thirty specimens contained bilirubin, averaging 50, the maximum being 100, 14 contained bile salts, 12 patients were jaundiced and 6 had bile in the urine, 19 had urobilin in the blood and 39 in the urine It is this group that provided the large number of specimens with urobilin in the blood, but in only those cases in which the specimen was taken early in the course was the urobilin found Urobilin was found to appear in the blood very early in the course of

the disease — in several instances preceding jaundice It also disappears very rapidly — from the blood several days to a week before it is absent from the urine In but four instances was urobilin found on two successive days The severity of the infection was not an apparent factor on two successive days The severity of the infection was not an apparent factor in the presence of urobilinemia out of 15 patients who showed it, ten recovered

Examination of the stool in pneumonia cases showed an increase in bile output for several days, usually during the period of urobilinemia or jaundice

Malaria —Five cases of malaria were examined and six specimens taken Five out of six contained bilirubin, and none contained bile salts The absence of bile salts is significant, but the numbers are too small to justify much speculation The output of bile in the stool in three of this group was increased, in the other two no measurements were taken

Ectopic Pregnancy —Three cases of ectopic pregnancy were found and four specimens examined Bilirubin was found in all four specimens, but only in small amounts, none of the patients was jaundiced Bile salts were present in but one The stools showed no increase in bile output

Teniasis —Three cases of *Dibothriocephalus taeniasis* were found and four specimens examined Bilirubinemia was present in all, but only one patient was jaundiced Bile salts were present in the plasma of two out of the three patients In all three the stools showed an increase in bile This group cannot be distinguished from primary anemia by the behavior and distribution of bile

Plumbism —Four cases of chronic lead poisoning were found and three patients had bilirubin in the plasma, but all four had bile salts in the plasma Bilirubin was present in small amounts and none of the group of patients was jaundiced The urine in all was negative, the stools also The presence of bile salts in this group may be of some importance

Primary Anemia —Thirty-four cases of primary anemia were examined and 42 specimens taken Thirty-two specimens of plasma contained bilirubin and 13 of the patients were jaundiced Bilirubin was not found in the urine of any The bilirubin in the blood in 10 specimens was 50 or over Bile salts were found in 24 plasmas, and in 2 urines Urobilin was found in 20 urines, the stools showed increase in bile output in all that were satisfactorily investigated This group is characterized by a particularly high degree of cholemia without jaundice or choluria, and by a marked retention of bile salts in the blood This is essentially the same as previously reported

Recently it has been found that in primary anemia there is a marked impairment of kidney function, and the possibility of the choluria in primary anemia being due to renal impairment must be considered I therefore examined the plasma of 16 nephritics to determine somewhat the rôle of renal impairment in the accumulation of bile in the blood These plasmas are uncommonly clear and colorless Only 2 contained bilirubin, one at 5, and one at 10 This in some cases can be explained by the retention of water in the plasma Seven specimens contained bile salts None of the patients were jaundiced and the urine in all was negative It is quite significant that 7 patients without apparent cause had increased amounts of bile salts in the blood, and it is very probable that the renal impairment in primary anemia is an important factor in the accumulation of the salts in the blood

Secondary Anemia—Seven cases of severe secondary anemia were examined The plasma in six patients contained very small amounts of bilirubin, but none contained bile salts Four of these patients were thought to be jaundiced, but this is explained by the great pallor The urine of all was negative, the stools of all this group that were satisfactorily investigated showed a slight diminution of bile output This fact is significant only when we compare this group with the primary anemias due to *Dibothriocephalus*

The plasma of twenty-two perfectly normal persons was examined and thirty-four specimens taken Eight specimens contained bilirubin and four bile salts The urine in all was negative In connection with Dr Christie, who has examined the blood recently of many normal persons in his work on renal function, an opportunity was given me to obtain a limited number of specimens at intervals during the day, in relation to taking food and abstaining from food, but thus far the material is too limited to be of value, except that nothing radically contradictory has been found

EXPERIMENTAL INTESTINAL OBSTRUCTION

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REVIEW OF THE LITERATURE

The following experimental work was begun in the summer of 1915, at the suggestion of Dr A J Carlson, as a further contribution toward the explanation of the cause of death in acute ileus, or high intestinal obstruction The theories propounded to explain the fatal issue in high intestinal obstruction in man, studied comparatively in animals, are almost as diverse as the number of workers in the field Chief among the theories that have been submitted since systematic experimentation was begun in this line may be enumerated the following

1 *Splanchnic paresis,* or disorder of the nervous mechanism controlling the cardiac and vasomotor systems, due to irritation of the nerves in the intestinal wall

2 *Bacterial infection,* or outward passage of bacteria through the intestinal wall, invading the peritoneum and producing a peritonitis, or invading the blood and lymphatics and producing a septicemia

3 *Autointoxication,* or the absorption of various poisons from the intestinal tract

This, at present the most popular general theory, embraces a diversity of modified forms, variously seeking the intoxication (1) in the stagnation of food materials and secretions, (2) in a bacterial origin, (3) in the absorption of poisonous substances elaborated by the intestinal mucosa or produced by a perversion of the intestinal secretion itself, (4) in tissue or mucosal autolysis, (5) in a disturbance of balance between the intestinal secretions, (6) in the abnormal absorption of poisons, as a result of damage to the intestinal wall

4 *Dehydration,* or the excessive loss of water from the tissues through drainage into the intestinal lumen, followed by vomiting

Braun and Boruttau[1] are among the most recent champions of the theory of *splanchnic paresis* They consider the source of the trouble

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* Submitted for publication Dec 6, 1917
* From the Hull Physiological Laboratory, University of Chicago

* This work was completed prior to the similar work of Dragstedt, Moorhead and Burcky, reported from the same laboratories recently in the Journal of Experimental Medicine (March, 1917, **25**, 421), but extraneous duties have unfortunately precluded the preparation of the work for publication until the present time

1 Braun and Boruttau Deutsch Ztschr f Chir, 1908, **96**, 544

to lie in the interference with the inherent nerve plexuses of the intestinal wall, this resulting in the stagnation of blood in the splanchnic region, in the enormous transudation of fluid into the intestine, followed by persistent vomiting, and leading finally to cerebral anemia and death McLean and Andries[2] concur with these authorities and believe that the paralyzing effect on the sympathetic system is due to the marked overdistention caused by the gradual accumulation of gas in the lumen

Wilkie[3] also subscribes to the hypothesis of vascular depletion, and believes that the higher mortality of acute high obstruction is due to the marked degree of vomiting in these cases, low obstruction being less fatal because of the greater reabsorption of fluid

Hartwell and Hoguet[4] likewise recognize the rôle played by overdistention of the intestine, and particularly by the loss of water from the tissues, but do not concede sympathetic reflexes and cerebral anemia as the all important factors in the fatal outcome Rather, they recognize the symptoms common to these cases as those characteristic of any severe sickness At any rate, the theory of strict sympathetic nervous reflexes or intrinsic splanchnic irritation is now no longer held tenable, since in duodenal obstruction, in which there is often very little dilatation, the animals soon succumb, but survive low iliac obstruction (in which there is marked overdistention), or survive even the isolation of the intestine from its various ganglia

Among the leading advocates of the theory of *direct bacterial infection* or septicemia we find the names of Borszeky and Genersich,[5] who base their conclusions on the finding of *B coli* in the peritoneal cavity and blood after ligation of the colon and of the small intestine Murphy and Vincent,[6] however, dismiss the theory as untenable, in that no peritonitis can be demonstrated in many cases of intestinal obstruction Hartwell, Hoguet and Beekman,[4] while conceding the presence of *B coli* in the blood from intestinal disturbances much less severe than obstruction, and the incidence of peritonitis even in intestinal obstruction without perforation, yet regard the invasion of the peritoneum most often as simply a terminal event, especially so in strangulation Thus, cultures made immediately after death in high obstruction failed to show the slightest bacterial invasion of the peritoneum, blood, liver or spleen

Howell,[7] however, presents the most unique defense for the theory of direct bacterial invasion He assumes that the complex in high

2 McLean and Andries Jour Am Med Assn, 1912, **59**, 1614
3 Wilkie, D P D Brit Med Jour, 1913, **2**, 1064
4 Hartwell, Hoguet and Beekman The Archives Int Med, 1914, **13**, 701
5 Borszeky and Genersich Beitr z klin Chir, 1902, **36**, 448-527
6 Murphy and Vincent Boston Med and Surg Jour, 1911, **165**, 685
7 Howell, J Brit Med Jour, 1913, **2**, 1645

intestinal obstruction is initiated by the increased permeability of the intestinal wall to bacteria, and that consequently the site of production of the poison and its absorption is the peritoneal cavity The bacteria, he contends, cannot be put in evidence outside the intestinal lumen, because it is one of the functions of the peritoneum to destroy bacteria In support of his theory, Howell cites the ease with which the migration of *B coli* from the colon and cecum may normally occur across the body cavity, with resultant infection of the bladder, of quiescent ovarian cysts and pyosalpinx—but without producing peritonitis

Among the various sources of autointoxication sought in explanation of the symptoms of ileus, the absorption from the intestines of the products of stagnated foodstuffs and intestinal secretions early attracted the attention of the physiologist Bouchard was the first to emphasize this point of view, contending that the stagnation of intestinal contents resulted in the production of poisons which have a special affinity for the nervous system

Likewise von Albeck[8] found that the products of putrefaction in strangulated loops were highly toxic on injection, reproducing the typical symptoms of obstruction He classified them with the group of putrefactive poisons

In this connection, Draper[9] at the outset of his work emphasized the retention of the biliary secretions as a factor in the production of toxemia in duodenal obstruction But later experiments have led him to abandon this theory

Later investigations, however, have shown the rôle played by food stagnation to be negligible, inasmuch as neither preliminary starving of the animal, nor thorough irrigation of the isolated loop results in any marked prolongation of life

Among the most noted earlier investigators to seek the autointoxication in a *bacterial source* are Clairmont and Ranzi,[10] who produced low, simple obstruction in dogs and cats They found that the injection of the filtered contents, as well as the injections of cultures grown from the intestinal contents, always produced the typical symptoms of ileus

Later McClure[11] and Macallum repeated the work by means of simple ligation or by isolation of loops at various levels, carefully eliminating stagnant food and intestinal secretions as possible factors The loops became greatly distended and incubated enormous numbers of bacteria, death usually supervening in a few days, often independently of perforation and peritonitis Injection of the filtered contents of the

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8 Von Albeck Arch f klin Chir, 1901, **65** 569

9 Draper-Maury, J W Am Jour Med Sc, 1909, **137,** 725, *Ibid*, Jour Am Med Assn, 1910, **54,** 5

10 Clairmont and Ranzi Arch f klin Chir, 1904, **73,** 696

11 McClure, R D Jour Am Med Assn, 1907, **49,** 1003

loop into the peritoneal cavity of normal dogs reproduced the typical symptoms of ileus but did not cause death These experimenters ascribed the symptoms to the absorption of bacterial poisons, the loops being impermeable to the bacteria

Murphy and Brooks[12] are the most recent and well known advocates of the theory that death after intestinal obstruction is the result of a bacterial toxemia, independent of peritonitis or septicemia They are chiefly distinguished for the additional modification that the factors which make absorption possible are more important than the factors which produce the toxin The toxic substance, therefore, is assumed to pass only through abnormal mucous membrane The chief factor permitting this abnormal absorption consists of an interference with the circulation of the obstructed intestine Thus, believe they, it is the marked secretory activity of the duodenum and jejunum, with the resultant rapid distention and circulatory disturbance, which results in earlier and severer symptoms than similar obstruction in the ileum The symptoms and pathologic lesions following administration of such loop contents are found to be identical with those following injection of certain ptomain poisons

The chief arguments advanced against the bacterial theory of intoxication are based on the fact that the onset of the symptoms in high intestinal obstruction is too rapid for a bacterial toxemia, and that high obstruction is more severe and fatal than low, although a much scantier bacterial flora is found in the high intestine

Chief among the opponents of the theory of bacterial intoxication are Whipple, Stone and Bernheim,[13] who contend that the production of the toxin is due to a *perversion in the activity of the secreting mucosa* of the duodenal or high intestinal loops, this taking place even in the absence of demonstrable changes in the mucosa

Roger[14] had already referred the source of the toxin to the activity of the intestine itself, and demonstrated the presence of a proteose in the occluded loops, but claimed that the products of the normal, unobstructed intestine were more toxic on injection than of the obstructed Davis[15] similarly has found that products of washed out, apparently normal draining loops produce the symptoms of ileus on injection This leads him to ascribe an excretory function to the intestinal mucosa as the source of the toxic substance

Whipple,[16] however, finds that preparations of the normal intestinal mucosa are without marked toxic effects on injection He holds that

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12 Murphy and Brooks The Archives Int Med, 1915, **15,** 392
13 Whipple, Stone and Bernheim Jour Exper Med, 1913, **17,** 286
14 Roger and Garnier Presse med, 1906, **14,** 325
15 Davis, D M Bull Johns Hopkins Hosp, 1914, **25,** 33
16 Stone, Bernheim and Whipple Ann Surg, 1914, **59,** 714

the chief source of the elaboration and absorption of the poison is in the mucosa, and not the lumen, citing in chief support the fact that even dogs with draining loops may die, or if surviving, develop an immunity to the toxin, and that loop products on injection are fatal when the mucosa has remained intact, but are innocuous when the mucosa has been destroyed by sodium fluorid

Gurd,[17] while endorsing Whipple's position as to the active rôle of the duodenal mucosa, contends that the substance responsible for the toxic symptoms is a result of *tissue autolysis* His experiments indicate that even autolyzed normal mucosa is just as toxic as preparations of loop mucosa, thus controverting Whipple's results

More recent investigations into the nature of the toxic substance would seem strongly to support Whipple's point of view Thus the observations of Peterson, Jobling and Eggstein[18] on the serum changes that develop during acute experimental pancreatitis indicated that the shock and death are due to an intoxication from absorbed protein split products Whipple, Rodenbaugh and Kilgore,[19] by similar observations, have put in evidence the same increase in noncoagulable blood nitrogen in acute intestinal obstruction, and point out that the injection of pure proteose will reproduce the same blood changes as intestinal obstruction Whipple[20] claims that bacterial activity is not necessary for the formation of this toxic proteose, which is precipitable from loop preparations by the addition of five volumes of 95 per cent alcohol

Chief among the defenders of a purely physiologic cause of the intoxication, as opposed to a pathologic or bacterial, is Draper,[9] who believes, as Vidal[21] had formerly contended, that the symptoms are referable to a *disturbance in the balance between the secretions* of the duodenum and jejunum He found that obstructions within a limit of 35 cm from the pylorus were always incompatible with life, and refers death to the retention of some toxic secretion, probably pancreatic, which normally would be detoxified lower down by protective jejunal or ileal antiferments

Matthews[22] by a somewhat similar series of experiments, in which he eliminates all pancreatic and gastric secretions as well as biliary, was led to arrive at a parallel conclusion, as to the necessity of a mutual interaction between the secretions of the duodenum and jejunum His experiments seemed to indicate that the retention even of a small patch

17 Gurd, F B Jour Infect Dis, 1914, **15,** 124
18 Peterson, Jobling and Eggstein Jour Exper Med, 1916, **23,** 491
19 Whipple, Rodenbaugh and Kilgore Jour Exper Med, 1916, **23,** 123
20 Whipple, G H Jour Am Med Assn, 1916, **67,** 15
21 Vidal, E Rev de chir, 1900, **22,** 521
22 Matthews, S A Jour Am Med Assn 1910, **55,** 293

of the duodenum, transplanted into the jejunum, was sufficient to prolong life in cases of obstruction

Draper,[23] moreover, applied his hypothesis to feeding experiments, and seemed to get a prolongation of life in his dogs by feeding supposed neutralizing preparations of jejunal and ileac cells from normal animals More recent experiments,[24] however, have failed to put in evidence any appreciable prolongation of life He points out, however, the significant relation between the digestive power of the different parts of the alimentary tract and the toxicity or acuteness of symptoms following obstruction, symptoms thus being less marked in the regions of the esophagus and colon

Recently Sweet, Peet and Hendrix[25] have reaffirmed Draper's point of view, pointing out in support the close analogy between pancreatitis and high duodenal obstruction They concur with Whipple in conceding the presence of a toxic proteose, but claim, however, that this can arise only in the duodenum from pancreatic or gastric digestion, and never in the jejunum, which secretes only erepsin

Hartwell and Hoguet[26] take issue with the foregoing authorities and oppose the views that the absorption of a toxin can occur in *uncomplicated* intestinal obstruction, claiming that the symptoms are always due to the *presence* of *lesions* which favor the *abnormal absorption* of toxins normally present, or that have resulted from stagnation They believe these lesions are produced by the irritating effect of retained secretions or by disturbance in the circulation such as follows local strangulation (on inversion of the cut ends of loops), or follows overdistention from retained secretions

They object further to Whipple's interpretation of the symptoms on the ground that the symptoms following the injection of loop contents are different from those following their assumed absorption, that, moreover, substances which on injection are toxic may actually be harmless on absorption, and that the permeability of the intestinal mucosa in uncomplicated obstruction is actually diminished, as determined by the absorption rates for strychnin and potassium iodid

These authors[4] propose, therefore, as an alternative hypothesis, that death in *uncomplicated* intestinal obstruction is always due to *dehydration* of the *tissues,* as a result of the transudation of fluids into the intestinal lumen, followed by vomiting In confirmation, they point out that life in such cases may be indefinitely prolonged by restoring the fluids through the subcutaneous injection of normal salt solution

23 Draper, J W Jour Am Med Assn, 1914, **63,** 1079
24 Draper, J W Jour Am Med Assn, 1916, **67,** 1080
25 Sweet, Peet and Hendrix Ann Surg, 1916, **63,** 720
26 Hartwell and Hoguet Am Jour Med Sc, 1912, **143,** 357

McLean and Andries,[2] as previously indicated, also believe the symptoms to be directly referable to depletion of the lymph and vascular systems, but believe death to be consequent, secondarily, on disturbance of the cerebral circulation

Whipple,[13] however, disposes of Hartwell's objection, in the assertion that absorption of the toxin may occur in uncomplicated obstruction with a normal, intact mucosa He explains the loss of fluid as a symptom common to any intoxication, and believes hypodermoclysis effective in prolonging life simply because it promotes diuresis Moreover, Bunting and Jones,[27] who concur with Whipple's point of view, have found from experiments on rabbits that loss of fluid by vomiting is only a terminal event, and that, furthermore, the secretion of fluid into the duodenal loop is quite negligible Finally, it has been found that the decrease in water content of the tissues is not alarmingly excessive in these cases, amounting to only one tenth of the body weight, or the equivalent of that produced simply by seven days of fasting, or four days of salivation through pilocarpin

Finally, of great, perhaps decisive, importance in this connection, is the work of Dragstedt, Moorhead and Burchy,[28] recently reported The distinctive merit of these workers lies in their success in securing complete sterilization of the isolated loops by washing with ether The closure of such loops was found compatible with life for indefinite periods, even when involving great distention and marked necrosis, and when completed by ligation of all the blood vessels to the loop Their findings would seem to indicate two distinct but complementary factors in the toxemia first, the presence of bacteria, of whatever nature, second, the presence of necrotic tissue, as a substrate for the elaboration of the fatal toxins through the action of these bacteria

Definition—Ileus is defined, clinically, as a complex of symptoms consisting in pain, tympanites, vomiting, and inability to get a bowel movement In experimental ileus, however, owing to the experimenter's control of conditions, any or all of these symptoms may be practically absent Indeed, it would seem that even obstruction may be absent, as in the experiments of Whipple,[16] where well drained, isolated segments of the intestine were incompatible with life All forms of ileus, however, are characterized by an acute toxemia So that ileus might be defined comprehensively, therefore, as a disturbance in the functional or anatomic integrity of the intestinal tract, associated with a profound intoxication

Working Theory—Now this intoxication, of whatever origin, whether due to increased permeability and so increased absorption, to

27 Bunting and Jones Jour Exper Med, 1913, **17,** 192

28 Dragstedt, Moorhead and Burchy Jour Exper Med 1917, **25,** 421

dehydration, to tissue autolysis, or to perversion of secretion, is sufficiently explained initially on the basis of the infection theory, it would seem, if it can be shown only that the presence of bacteria is necessary to initiate the sequence of changes that lead to the final absorption of a poison, or to both its production and absorption The present experimenters have tentatively accepted this point of view as a working theory, believing that the solution of the problem resolves itself into a task of eliminating all bacteria as a possible factor in the change

Methods—Obstruction was uniformly and consistently produced by completely isolating about 20 cm of the first part of the jejunum, the continuity of the intestinal tract then being restored by direct end-to-end union or by lateral anastomosis This permits free feeding of the animal, and so reduces to a minimum starvation and loss of fluid as essential factors in the production of symptoms It also permits the normal free drainage of the biliary and pancreatic secretions, precluding the formation of a blind pouch in the duodenum, which Sweet[25] claims is of itself sufficient to produce symptoms of obstruction

As a part of the routine, a preliminary period of starvation was given the animal, the stomach and bowels being completely evacuated finally by means of apomorphin To further minimize the bacterial flora, thorough washing of the loop with sterile normal saline was usually done after section The loops were then completely obstructed by inverting and suturing over the ends, or only partially by closing one end and permitting free drainage from the other

Symptoms—The development of symptoms in our dogs paralleled closely those observed by other writers During the first day and a half, after the immediate postoperative effects have worn off, the animal is fairly alert and lively, drinks water eagerly and even partakes of a little milk A considerable amount of vomiting is evident from the outset, however, especially after drinking, the vomitus being bile tinged Toward the end of the second day the animal becomes pinched and sick in appearance, dull and apathetic, refusing food, and manifesting a disposition to lie quiet or sit in an immobile position If there is a tendency to movement, the animal's gait is stiff and uncertain, due to marked lack of flexibility of the muscles A conspicuous shivering or tremor of the muscles then supervenes, and the animal almost invariably passes away at the end of seventy-two hours, with all the symptoms of profound shock

Contrary to the observations of a few workers, most of our dogs gave no evidence of marked colic or pain, nor presented any marked abdominal distention, the abdomen, indeed, being generally scaphoid in contour Nor were tonic or clonic spasms in evidence as a terminal event

An objection of Hartwell's[4] is pertinent in this connection, namely, that the symptoms arising from the injection of loop contents are not necessarily the same as those arising from its assumed absorption in the loop Thus, Kukula, Clairmont and Ranzi, and von Albeck have found in general that injections of filtered loop contents produce symptoms of violent vomiting and diarrhea, quickening of the respiration, and tonic and clonic spasms Though we have not done extensive experimenting along this line, these symptoms seemed to simulate more closely those of anaphylactic shock than of septic absorption Thus, in one instance, intravenous injection of 6 c c of the centrifuged supernatant fluid produced violent vomiting of almost pure bile, purging and tenesmus, general restlessness and tendency to scratch the nose, violent tonic and clonic spasms, and finally complete collapse and death—all within fifteen minutes after injection Though the pathologic findings are somewhat similar, namely, a marked hemorrhagic enteritis of duodenum and jejunum, yet the symptoms certainly do not closely resemble those due to complete obstruction

Pathology—Necropsy invariably revealed evidence of marked splanchnic congestion, especially in the duodenum and jejunum, associated with the presence usually of a mucopasty brown material in the lumen The stomach was usually congested to a less marked degree, and contained frequently a light bile or blood-tinged fluid The spleen and liver were swollen and congested and the kidneys at least gave evidence of cloudy swelling The loop itself was usually greatly distended, markedly reddened and the walls swollen The mucosa of the loop was usually much necrosed and invariably ulcerated, usually in the most dependent part, opposite the mesentery The contents, which often had partially escaped through the ulcer into the peritoneal cavity, consisted of a characteristic thick, blood tinged brown fluid This on microscopic examination revealed enormous numbers of bacteria The peritoneum was usually mildly or acutely inflamed, the body cavity sometimes containing a thin, reddish, inflammatory transudate or the escaped contents of the loop

The Rôle of Peritonitis—The typical picture of ileus is, therefore, usually somewhat complicated by a terminal peritonitis, death being precipitated perhaps by the sudden outpouring of virulent toxins from the ruptured loop Indeed, some investigators, such as Wilkie,[3] have never found death uncomplicated by perforative peritonitis, and Sweet[25] believes that overdistention and rupture are always the actual causes of death Experiment 2 represents a typical case

Experiment 2—Operated on July 5, 1915, 8 a m Weight, 6 kg Sex, female (black and white)

Operation—Isolated about 20 cm of intestine just below duodenum, ends inverted and sutured over, lateral anastomosis made between duodenum and jejunum, loop not washed

July 6, 1915 Dog is active, walking around, drinks water, vomits yellowish fluid, had slight tremors in the morning

July 7, 1915 Dog looks sick, averse to drinking, vomits bile-stained fluid. Dog in profound shock, but still alive at 9 30 p m

July 8, 1915 Found dead in morning, brownish fluid oozing from dog's mouth

Necropsy—Weight, 5 225 kg Suture line of anastomosis in good condition, lungs edematous, liver enlarged and congested, kidneys, cloudy swelling, spleen congested, stomach hyperemic, duodenum markedly congested, jejunum congested, but to lesser degree, isolated loop dilated, thickened, and greatly reddened, ulcers, with perforation in several places, peritoneal cavity contains a large quantity of brownish fluid having a foul odor The peritoneum is acutely congested

Here, however, it will be seen that, though the animal died from a terminal peritonitis, the onset of the symptoms was too rapid to explain initially on the basis of peritonitis

To eliminate peritonitis as a complicating factor and so to secure an unadulterated picture of ileus, we conceived the plan of placing the closed loop extraperitoneally immediately beneath the skin, leaving an opening in the peritoneum and fascia just large enough to admit the mesentery without strangulation of the vessels Experiment 15 is typical of the results, and shows that toxemia develops even with a peritoneum thus protected, and that the symptoms are relieved rather than aggravated when the loop perforates and free drainage obtains, even into the subcutaneous tissues These loops, though markedly distended and congested, assume their initial condition, exhibiting active peristalsis and secreting a clear fluid

Experiment 15—Aug 6, 1915, 8 a m Weight, 4 760 kg Sex, female, black and tan, starved eighteen hours

Operation—Twelve cm jejunum resected and ends closed (without previous washing), continuity of intestinal canal restored by an end-to-end anastomosis and loop placed extraperitoneally under skin, without drainage

Aug 7, 1915 Dog fairly active and takes food, marked distention of loop under skin

Aug 8, 1915 Dog looks sick and dull, refuses, still a marked distention of loop under skin

Aug 9, 1915 Dog active, eating meat, loop collapsed under skin, contents evidently having been absorbed, as there is no exudation through suture

Aug 10, 1915 Active, eating meat greedily, loop still collapsed, and no ill effects apparent

Aug 11, 1915 Active, eating meat, loop collapsed, but a serosanguineous fluid now apparent oozing from the suture An opening was made for drainage and a part of intestinal loop exposed, the loop appears normal in color

Aug 14, 1915 Loop has been draining a clear serous fluid, dog discarded as he exhibited no further symptoms of interest

In a similar manner, aspiration of the contents of a closed loop leads to a subsidence of the symptoms after their onset This is accomplished by suturing the loop to the abdominal wall, leaving an opening in the abdomen just large enough to make the loop accessible for aspi-

ration Thus, while aspiration in the following experiment (11) did not prevent death, which was due to other complications, yet it prevented the development of acute symptom and prolonged life far beyond the average period

Experiment 11—July 27, 1915, 10 30 a m Weight, 3 520 kg Sex, female, pup, black and white, starved forty-eight hours

Operation—Twenty cm jejunum isolated, washed with sterile, normal saline and ends inverted, end-to-end anastomosis made and loop sutured into opening in abdominal wall for purpose of aspiration

July 28, 1915 Comparatively active, drinks water eagerly, wound of good appearance, small quantity of green vomitus in cage

July 29, 1915 Not very active, dull, refuses milk, 4 p m about 50 c c of serosanguineous fluid containing a caseous brown sediment aspirated from loop

Injection experiment 3 c c of centrifuged supernatant fluid injected intravenously into both a collie and a bulldog, each weighing approximately 8 kg, no pronounced toxic effects, excepting defecation and vomiting, developing a few minutes after injection Dog soon recovered

July 30, 1915, 10 a m About 75 c c of fluid again aspirated from loop, this time being clear, serous in character Symptoms are no worse, but dog still refuses food, a trace of distemper, the eyes and nostrils containing pus

July 31, 1915 Dog found dead Postmortem revealed that suture line of anastomosis had perforated, causing fatal peritonitis, loop, however, not perforated and of normal appearance, but contains a large amount of pasty brown substance

Weight, 2 860 kg

This is confirmed, further, by the development of toxemia when freely draining loops are closed, as in Experiment 43 following, in which the symptoms began to subside as drainage was reestablished by partial leakage around the tube, and ceased altogether when the clamped tube was pulled out An analogous case is seen in Experiment 61, in which the draining loop accidentally became closed and caused death, necropsy revealing a normal peritoneum

Obstruction by postoperative intussusception occurred in a few of our dogs, by a curious coincidence in the neighborhood of the resection, this resulting perhaps from operative trauma While the necropsy in these cases revealed the usual findings of ileus, the peritoneum presented a normal appearance, as in Experiment 20

Experiment 20—Aug 16, 1915, 1 p m Weight, 5 560 kg Sex, female, brindle bull, starved forty-eight hours

Operation—Twenty cm of jejunum isolated, washed with normal salt solution, end-to-end anastomosis made and isolated loop left with both ends open to drain into the peritoneal cavity

August 17 Dog is active

August 18 Very active, takes milk

August 19 Fairly good condition, but less active

August 20 8 a m, very dull and inactive, refuses to eat, 5 p m, found dead

Necropsy—Liver greatly congested, stomach hyperemic, peritoneum, normal, anastomosis union good but suture line hyperemic, loop collapsed and with a normal healthy appearance, one end adherent to intestines, other end

closed by omentum, a thick yellow fatlike substance exuding when end was squeezed Jejunum at distance of about 12 inches from anastomosis almost 18 inches of proximal part of jejunum had telescoped into part below, section intussuscepted greatly congested

This would seem to confirm the observations of a majority of the experimenters that all the symptoms and pathologic findings of ileus may be present in the absence of peritonitis

The Rôle of Washing in Loops—As previously intimated, efforts were especially directed toward eliminating as far as possible the bacterial content of the loops, usually by washing with sterile normal saline Usually cultures in beef broth made from sections of the mucosa before washing showed only a moderate growth, while those made afterward were usually negative But all attempts to arrest the process were futile, since in the washed as well as in the unwashed loop the symptoms always pursued the same course, ending usually in perforative peritonitis and death of the animal

Although this attempt at sterilization was incapable of completely arresting the process, at least it served to delay the development of symptoms and onset of death Thus the average length of life as found for dogs with unwashed loops was 48 hours, and for washed, 72 hours This finding parallels qualitatively that of Whipple,[13] who found in double duodenal ligation a value of 48 hours for washed loops and from 24 to 28 hours for unwashed loops

The Rôle of Dehydration—The loss in weight of our dog in three days averaged about 13 per cent of the total body weight Starvation could not be an important factor in the reduction, since the animals could retain food a part of this period Furthermore, Hartwell[26] has found that a dog fasting two weeks loses only 29 per cent of its body weight, receiving meanwhile saline injections As vomiting in our dogs was negligible, and transudation or secretion into the loop inconsiderable, the loss seemed to be due to inability to maintain a balance between liquid intake and output The average loss observed by most investigators during this period is about 10 per cent, being negligible in amount, or that resulting alone from seven days of fasting (Draper[23])

TABLE 1—WEIGHT LOSS DURING OBSTRUCTION EXPERIMENTS

Dog	Weight Before, Kg	Weight After, Kg	Life Period, Days	Loss, Per Cent
2	3 520	2 860	4	18 7
3	7 520	6 440	3	14 8
4	7 840	6 400	4½	18 0
5	7 060	6 440	1½	9 0
6	3 440	3 200	2	7 0
7	7 780	6 700	2½	14 0
10	4 260	4 160	2	2 4
11	3 520	2 860	4	19 0
Average			3	13 0

The Rôle of Overdistention—Some investigators, notably Hartwell[4] and Sweet,[25] emphasize the rôle played by overdistention and conse-

quent strangulation as a cause of death, resulting directly from secondary perforation and peritonitis Others such as Whipple[29] and Draper[9] have found the loop to behave in various ways, death resulting even when the loops were almost completely collapsed We have observed a similar diversity of behavior in our dogs Thus, while typically the loop becomes tremendously overdistended and gangrenous in appearance, culminating finally in perforation and peritonitis, yet a few were found collapsed, possessing an apparently normal mucous membrane and containing only a characteristic pasty brown substance, as in Experiment 61

Furthermore, Experiment 43 shows that even tremendous overdistention is not necessarily incompatible with life, this dog living several days and only dying from other causes

EXPERIMENT 61 —Aug 7, 1916, 2 p m Sex, female, mongrel, medium brown, starved twenty-four hours

Operation —Isolated 20 cm jejunum, restored continuity by lateral anastomosis, closed one end of loop A small rubber tube was pursestringed into the other end, and with tube, sutured into abdominal wall for drainage

August 8 Dog fairly active, drinks water

August 9 Dog inactive, listless, and drowsy, refuses food

August 10 Found dead in morning

Necropsy —Peritoneum normal appearance, lateral anastomosis, no leak, no inflammatory findings, liver greatly congested, duodenum and jejunum markedly hyperemic, presenting the typical findings of ileus, isolated jejunal loop not distended, mucosa slightly congested, but otherwise normal, free from ulceration, lumen partly filled with a characteristic semipasty brown substance

The Rôle of External Drainage —Failing to secure perfect sterilization of the loop by washing with normal saline, we adopted the method (also employed by various workers in the field) of drainage to the exterior, in the hope that the loop would finally become sterile, and so permit closure without the development of toxic symptoms Whipple[29] has found that even such dogs draining externally usually die from ileus in from three to six days, and attributes death to the absorption of a toxin or perverted secretion from the mucosa of the loop Our dogs, however, continued to drain indefinitely without the development of toxic symptoms, death always being accounted for from other causes than ileus (as in Table 2)

The results shown in Table 2 followed despite the fact that the skin usually retracted and closed over the loop after a week or ten days, absorption taking place then not only from the mucosa, but also from the lumen through the subcutaneous tissues Sweet,[25] however, has given a plausible explanation of Whipple's results, in that by his method of double ligation a blind pouch is formed in the duodenum,

29 Whipple, Stone and Bernheim Jour Exper Med, 1914, **19**, 144

from which toxins are absorbed, and excreted secondarily, perhaps, into the draining loop

TABLE 2—RESULTS OF EXPERIMENTS WITH EXTERNAL DRAINAGE

Dog	Length of Life, Days	Cause of Death
8	136	Killed for necropsy
9	4	Postoperative intussusception of jejunum
10	15	Unknown
12	30	Infection and gangrene of laparotomy wound
15	8	Discarded after this period
25	120	Killed for necropsy
26	30	Pneumonia
32	30	Pneumonia
33	105	Killed for necropsy
35	60	Killed for necropsy
38	13	Ileus, due to intussusception of isolated loop
61	3	Ileus due to accidental closure of draining loop

Our draining loops had apparently closed, but laparotomy always showed them in a collapsed state, and careful testing with sterile saline generally revealed a minute opening through which drainage could be effected (as in Experiment 25)

Experiment 25—Aug 24, 1915 Sex, female, brown bull pup

Operation—Twenty cm jejunum isolated, one end inverted and closed, and open end anchored into opening in abdominal wall for external drainage, the mucosa being everted, end-to-end anastomosis to restore continuity of jejunum

August 25 Dog quite active, drinks freely of milk

August 26-31 Continues active, eats meat, loop draining well, exuding a clear serous fluid

September 22 Dog quite active, loop has retracted from surface and skin closed over opening, the loop ceasing to drain to the exterior

October 23 Dog continues quite normal, exploratory laparotomy performed, inner end of loop found still closed and adherent along suture line of the end-to-end anastomosis, draining end found adherent to parietal wall at site of fistula and apparently closed Lumen of loop then inoculated with normal saline emulsion of scraping from jejunum of another dog, laparotomy wound then closed

October 25 Dog active, external site of fistula has opened up as a result of infectious process following inoculation, now oozing a thick, yellowish material

October 26 Active, eating heartily, fistula draining well

November 2 Dog active, fistula gradually healing over, secretion now serous in character

December 12 External fistula again entirely closed over

December 28 Dog posted, loop found as before, collapsed and of normal appearance Water injected into lumen and squeezed out through opening in laparotomy scar, so not completely closed

The Rôle of Intraperitoneal Drainage—In the further attempt to sterilize the isolated loop, we adopted a novel method (a method which so far had not been used by other workers, and which even we employed with a few misgivings), namely, *direct drainage into the peritoneal cavity* The loops were isolated as usual, washed with sterile saline and then returned to the abdominal cavity for direct drainage This was done in the hope that the few remaining bacteria in the mucosa might finally be overcome by the peritoneal fluids, and further-

more, that the process of self-inoculation so obtaining might lead to an immunity against intoxication on subsequent closure, or at least mitigate the effects of a perforative peritonitis

To our surprise the dogs continued active and healthy, even as in the cases of external drainage, very few of the dogs developing peritonitis so long as the loop remained open Exploratory laparotomy always showed the loop to be collapsed, in active peristalsis, and of normal appearance The ends were always invested by folds of the omentum, through which absorption took place

TABLE 3—RESULTS OF EXPERIMENTS WITH DRAINAGE INTO PERITONEAL CAVITY

Dog	Length of Life, Days	Cause of Death
17	3	Peritonitis due to direct infection from loop
18	13	Killed for examination
19	10	Peritonitis due to perforation by bone at site of anastomosis
27	3	Peritonitis as result of direct infection from loop
28	4	Strangulation and gangrene of jejunum, due to excessive operative manipulation
29	2	Perforative peritonitis, following laparotomy and closure of loop after thirteen days' drainage
30	21	Pneumonia
31	4	Perforative peritonitis, following laparotomy and closure of loop after fourteen days' drainage
34	15	Distemper
36	15	Distemper
39	4	Peritonitis, due to direct infection from loop
41	6	Peritonitis, due to leak at line of anastomosis of jejunum
42	3	Unknown

Results on closure, however, were quite disappointing, the animal running the usual course and suddenly succumbing, after two or three days, to perforative peritonitis (Experiments 29 and 31) Apparently the loop had not drained long enough to become completely sterile If the self-inoculation had resulted in any degree of immunity, it was certainly rendered inoperative by the sudden flooding of the peritoneal cavity with infectious material, although the development of the symptoms of ileus seems to be delayed, as in Experiment 31

EXPERIMENT 31—Sept 1, 1915 Weight, 8 54 kg Sex, male, black and white, starved twenty-four hours

Operation—Twenty cm jejunum isolated, washed with sterile normal saline, and dropped back to drain into peritoneal cavity, end-to-end anastomosis

September 2 Somewhat inactive, vomits water given

September 3 Dog continues quite active, eats meat greedily

October 16 Exploratory laparotomy done, loop collapsed and of normal appearance, undergoes active peristalsis, draining end invested by omentum, lumen patent and free from pus and detritus, both ends inverted and loop closed

October 17 Dog fairly active

October 18 Quite active, playing boisterously when let out of cage, drinks milk greedily

October 19 Not nearly so active, refuses milk, averse to jumping up on hind legs as though involved abdominal pain, found quite droopy in the evening

October 20 Dog found dead

Necropsy—Acute perforative peritonitis, peritoneum being inflamed and cavity filled with blood-tinged brown fluid, large perforation in middle of loop, in most dependent position, stained smears show enormous numbers of bacteria

The Final Evidence from Spontaneously Closing Loops—Since subsequent laparotomy and closure of draining loops involved more or less risk of infecting the mucosa, even if draining sterile, we improvised drainage permitting spontaneous closure in case the lop became sterile Tubes were inserted, as in drainage of the gallbladder, pursestringed, and the ends invaginated, the tube being withdrawn in a few days In this way we finally secured the much sought result—*a closed, isolated loop that was compatible with the life of the animal* (Experiment 43)

EXPERIMENT 43—Nov 20, 1915, 8 a m Weight, 6120 kg Sex, female, black and tan beagle

Operation—Twenty cm jejunum resected, one end inverted and closed, a rubber tube pursestringed and invaginated in the other end, and loop with tube anchored into abdominal wall for drainage to outside

November 20, p m Animal quickly recovered from operation and now fairly active, but tube is oozing a little blood

November 23 Dog quite active and tube still intact, now draining the characteristic thin clear fluid Tube clamped off to retain secretion and bandaged to retain in place

November 24 Dog looks toxic, being much less active and tending to remain in an immobile posture on haunches

November 25 Dog still toxic, but more active than yesterday

November 26 Dog again well and active, tube with clamp found completely pulled out, fluid now draining directly from invaginated end of loop

December 8 Dog found dead, having been killed last night in fight with another dog

Necropsy—Drainage outlet in skin healed over, draining end of loop closed, loop found enormously distended, being five or six times normal size, walls of normal appearance but somewhat thinned out, lumen contains a clear serous fluid resembling normal succus entericus Loop with contents placed in alcohol

As evidenced by its pugnacious disposition, this animal continued quite healthy, with a loop distended five or six times the normal size This was quite normal and its contents were inadvertently placed in alcohol, we were unfortunately prevented from examining it for the presence of bacteria It is hard to conceive of the loop closing in the presence of infection But whether bacteria were present or not, this solitary case at least justifies the thesis that *an animal may continue well and active with closed and overdistended isolated loops*

(A series of twenty dogs of this kind was run in the summer of 1916, but all the animals succumbed to heat and distemper Other experiments are pending)

SUMMARY

Our findings may be summarized briefly as follows

1 A majority of the dogs with isolated loops succumb to perforative peritonitis

2 But the development of toxic symptoms and death may occur independently of peritonitis

3 Symptoms on injection of loop contents are different from those due to absorption

4 Washing of the loop delays the development of symptoms and onset of death

5 Loss of body weight is not great enough to be an important factor in the process

6 Overdistention and strangulation are not necessary factors in the development of symptoms

7 Animals may live indefinitely with loops draining externally

8 Animals may live indefinitely with loops draining directly into the peritoneal cavity

9 Dogs may continue well and active with enormously distended loops that have closed spontaneously

We wish to express our thanks to Prof A J Carlson for suggestions and criticism, cheerfully given, and to Dr James J Moorehead, whose surgical skill greatly facilitated the execution of the work

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A NOTE REGARDING MYIASIS, ESPECIALLY THAT DUE TO SYRPHID LARVAE*

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DETROIT

Bruce[1] (1917) has recently published a paper reporting from Vancouver Island a very interesting case of vaginal myiasis in the cow due to the "rat-tailed larva" of the drone fly, *Eristalis* He does not say how many larva were found, but notes that the vagina was diseased and that a discharge was present In his paper, Bruce says "I am unable to find any reference to invasion of the vaginal cavity by the larvae of *E tenax* in either man or animals" As a matter of fact, Bruce's case is the second recorded case of this sort, the first having been published by Hall and Muir[2] (1913) Their record is as follows

> In the Bureau of Animal Industry collection of parasites there are also eight *Eristalis* larvae sent in from Laurel, Md, in 1909, with the statement that they were passed in a jelly-like substance from the vagina of cattle In correspondence relative to these specimens, Dr B H Ransom suggests to the sender
>
> Probably a diseased condition of the organ in which you found these larvae created an odor which attracted the flies to this particular place, with the result that they have deposited their young in the unusual location

The above record has been cited by Metcalf[3] (1916), but it is not at all surprising that the record escaped the attention of Dr Bruce The fact that we now have two records of the presence of *Eristalis* larvae in the diseased vagina of cattle instead of one record, however, does much to establish the validity of both records and the likelihood that similar occurrences do happen from time to time

Hall and Muir[2] listed a summary of seven published cases of myiasis in man due to larvae of the *Syrphidae* To this they add their new case and four cases from the files of the United States Bureau of Entomology, furnished through the courtesy of Dr L O Howard and

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1 Bruce, E A A New Parasite for Cattle The Larvae of *Eristalis tenax* L (drone fly), Jour Am Vet Med Assn, 1917, **1**, 66-68, Fig 1

2 Hall, M C and Muir, J T A Critical Study of a Case of Myiasis Due to *Eristalis*, THE ARCHIVES INT MED, 1913, **11**, 193

3 Metcalf, C L Syrphidae of Maine, Bull 255, Maine Agric Exper Sta, 1916

Mr R S Clifton, and one from the files of the United States Bureau of Animal Industry, furnished through the courtesy of Dr A D Melvin and Dr B H Ransom, to whose courtesy they were also indebted for the record of the case of vaginal myiasis Twelve of these were cases of gastro-intestinal myiasis and one (Leidy's) a case of nasal myiasis To the summary of human cases by Hall and Muir, I wish to add an unpublished case in man, for which I am indebted to the kindness of Dr Allen J Smith of the University of Pennsylvania and Dr F J Bardwell of Tunkhannock, Pa, and to note a subsequently published record by Iches[4] (1914), and three records of Austen (1912, not available), cited by Graham-Smith[5] (1914).

Under date of April 24, 1913, Dr Smith wrote me as follows

I have recorded here in our laboratory reports a case of *Eristalis* in the human stool, definitely regarded as *Eristalis*, and tentatively, for the same reason you assign in your case, *E tenax* (common occurrence of the fly) The specimens (two) were sent Sept 9, 1908, by Dr F J Bardwell of Tunkhannock, Pa, through the State Health Department (the bacteriological work of which was then done by this laboratory) as from the stool of B L, white, male, native, aged 18 No statement as to the condition of the subject and no account of the circumstances of recovery of the specimens were given, although doubtless Dr Bardwell can furnish them I note the specimens as 13 and 14 mm in length, respectively, 4 and 5 mm thick in anterior part, the "tail" as equaling the body length in the first, somewhat retracted in the second, tail curved anteriorly Dark brown, firm, apparently brittle, seven pairs of hook-bearing prolegs (numerous hooks arranged in curved rows) Dorsally at head end two pairs of hooks, the posterior the longer and directed forward, the anterior the smaller and directed backward On each side submedian row of indefinite tubercles, between which are a number of fine transverse ridges of the cuticle Indefinitely seven-segmented It has never been published

In response to a recent request for information in regard to this case, Dr Bardwell wrote me, under date of Oct 12, 1917, as follows

I remember the case you refer to very well About a year after that, he had the same thing again There is no doubt about it being a genuine case Creolin, one dram to quart of hot water, was the treatment The symptoms are intense irritation of the rectum

Iches[4] (1914) states that when traveling in the Argentine Republic he found in the entomologic collection which is under Dr Lahille's supervision, two rat-tailed larvae collected at Necochea in 1904, and was furnished the following history by Dr Lahille

A physician at Necochea was called in to attend a 7-year-old girl who complained of a pain in the rectum Nothing was detected on simple examination and the doctor ordered washing, which brought about no change He then gave a purgative, which caused the expulsion of the larvae, which were sent

4 Iches, L Un cas original d'hospitalisation rectale, Arch d parasitol 1914, **3**, 473

5 Graham-Smith, G S Flies in Relation to Disease Non-bloodsucking Flies Cambridge, 1914

to Lahille The two larvae measured as follows Body 12 5 mm long by 2 mm wide, tail 18 mm , body 11 mm long by 2 mm wide, tail 13 5 mm The color was dirty gray

Austen's cases of human myiasis due to syrphid larvae are noted by Graham-Smith[5] as follows "In England, Austen (1912) has met with two cases due to the larvae of a *Syrphus* or hover-fly, one case due to the 'rat-tailed maggot' of *Eristalis tenax* "

It would appear, then, that there are at least seventeen records claiming the presence of syrphid larvae in the digestive tract of man, one record claiming their presence in the nostrils of man, and two records claiming their presence in the diseased vagina of cattle

In passing, it might be noted that Blundeville in his book, "The Order of Curing Horse Diseases," published in 1609, says that a "bottee" has a "great head and small long tail like a needle" This is a very poor description of a bot and a fairly accurate description of a rat-tailed larva It suggests that Blundeville had seen rat-tailed larvae in horse manure, a favorite breeding place, and regarded them as bots which had been passed by the horse, and this may be a rather common error It is still a common error to regard free-living forms occurring in feces as parasites which have passed from the digestive tract Herms[6] (1915) says that the frequency with which the larvae occur in liquid excrement must lead to caution in accepting reports that they have been evacuated, and adds "The writer has on several occasions received specimens of 'rat-tailed' larvae which were said to have been evacuated by the 'double handful' and that the patient had 'steadily improved' thereafter"

As regards the species of syrphid involved in these cases, we may quote Metcalf's opinion

> I wish to emphasize the practical impossibility, at our present state of published knowledge, of referring larvae found in such circumstances to a definite species, or even to the genus, unless specimens are reared to the adult It seems to be the custom to refer any rat-tailed larva to *Eristalis tenax*, or at least to the genus *Eristalis* Such records, unless based on adults reared from the larvae, must, it seems to me, be discarded as of no specific importance I have examined a dozen species of rat-tailed larvae belonging to several genera, the separation of which is exceedingly puzzling and difficult, and any one of which might easily be mistaken for the larvae of *Eristalis tenax*

Hall and Muir[2] stated in regard to these rat-tailed larvae "Only an occasional pupa, and never a larva, survives the winter" Regarding this point, Mr E R Warren of Colorado Springs, Colo, a well-known ornithologist and mammalogist, wrote me, under date of March 18, 1913, as follows

> The latter part of February, 1902, I took from an outdoor tank at a fish hatchery near Crested Butte, Colo, a bunch of live rat-tailed maggots, which were identified by Dr L O Howard as *Eristalis tenax* He made no com-

6 Herms, W B Medical and Veterinary Entomology New York, 1915

ment as to the season when they were found, and perhaps did not understand that they were taken in winter

The tank was a wooden affair, perhaps 4 by 8 by 3 feet deep, in open air, not used for any special purpose, but the water from the hatchery flowed through it This water is taken from a spring and piped right into the building and flows through the hatching troughs, and hence out into the tank I have mentioned As the winters are cold there, 9,000 feet, the temperature of the water in the tank was probably not much above 32 F, but as it comes from the spring into the hatchery it is 45 F the year around

One sort of myiasis about which little of a specific sort seems to be published is rectal myiasis, due to blow-fly larvae, especially in sick and in moribund animals, and more especially where there is blood in the feces I have seen a few cases of this sort and had one case in the dog recently In this case the dog was being used to determine the lethal dose of an anthelmintic, and a resultant hemorrhagic gastritis was the source of the blood in the feces The day before this dog died, maggots were found to be crawling in and out of the anus To alleviate this condition, the dog was given a rectal injection of 1 c c of chloroform in 9 c c of castor oil On postmortem examination the following day, the rectum, colon and anal region were found free from larvae, but four larvae, dead when collected, were found in the small intestine It is possible that these four larvae had been driven back up the large intestine by the rectal injection and had entered the small intestine either before or after the death of the dog The dog had eaten nothing for several days, except a small amount of milk, and it appears more likely in this case that the larvae in the small intestine entered the body by way of the anus than by way of the mouth It suggests that occasional cases of gastric and enteric myiasis might be explained in this way in cases in which the evidence seemed opposed to the idea of infection by mouth Graham-Smith[5] (1914) has noted this as a possible mode of infection in man He says that "Babies left exposed in an uncleanly condition may become infested The larvae on hatching make their way into the rectum, and perhaps penetrate into the intestine"

A COMPARISON OF THE FUNCTIONAL AND ANATOMIC FINDINGS IN A SERIES OF CASES OF RENAL DISEASE *

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AND
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It is our purpose in this article to report a group of thirty cases of renal disease which have been studied by certain of the recently introduced methods of renal functional testing, including the estimation of the plasma chlorids Fifteen of these cases have come to necropsy, thus affording an opportunity of comparing the functional and anatomic findings The cases are classified into four main groups, with a few additional miscellaneous cases The important clinical findings and the results of the functional tests are tabulated in Table 1 The pathology of the kidneys from the cases coming to necropsy is tabulated in Table 2 A general discussion of the findings in each group is given in the text Detailed protocols of the individual cases are appended at the end of the report

METHODS

Blood pressures were read by the auscultatory method, the diastolic pressure being read at the end of the fourth phase The phenolsulphonephthalein figures represent in all cases the output in two hours after injection, allowing in the case of intramuscular injection an additional ten minutes for the appearance of the drug Catheterization was not employed routinely but only when there was evidence of retention The drug was injected into the lumbar muscles, as a rule, unless there was edema, in such cases it was given intravenously Blood for chemical study was taken from the vein at the elbow either before breakfast or four hours after a light breakfast For the estimation of the plasma chlorids and of plasma bicarbonate the blood was drawn directly into centrifuge tubes containing potassium oxalate crystals beneath paraffin oil and immediately centrifuged and the plasma pipetted from the cells Blood urea nitrogen was determined by the method of Van Slyke and Cullen,[1] total nonprotein nitrogen by the method of Folin and Denis,[2] using titration instead of

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1 Van Slyke, D D, and Cullen, G E A Permanent Preparation of Urease and Its Use in the Determination of Urea Jour Biol Chem, 1914, **19,** 211

2 Folin, O, and Denis, W New Methods for Determination of Total Nonprotein Nitrogen, Urea and Ammonia in Blood Jour Biol Chem, 1912, **11,** 527

nesslerization, plasma chlorids by the method of McLean and Van Slyke,[3] plasma bicarbonates by the method of Van Slyke[4] In all cases the figures for the phenolsulphonephthalein test represent percentile excretion for two hours, for the blood urea nitrogen and total nonprotein nitrogen, milligrams of nitrogen per 100 c c of blood, for the plasma chlorids, grams of sodium chlorid per liter of plasma, for the plasma bicarbonate cubic centimeters of carbon dioxid gas per 100 c c of plasma reduced to 0 C 760 mm Hg, and corrected for vapor tension The pathologic histology is based on tissues fixed either in Zenker's or Orth's fluid, sectioned in paraffin and stained with hematoxylin and eosin

Acute Glomerulonephritis and Early Chronic Nephritis —The series includes two cases of acute glomerulonephritis (Cases 1 and 2), one fatal, with necropsy, one with recovery Both cases exhibited elevation of blood pressure, increase of the urea or nonprotein nitrogen of the blood, marked increase of the plasma chlorids and a reduction of the plasma bicarbonates The pathology in Case 1 was that of an acute glomerulonephritis and acute suppurative interstitial nephritis

Case 3 was one of early chronic nephritis with a tendency to recurring acute attacks The renal functional tests in this case were normal at the time investigated The nephritis in this case appeared to be secondary to acute throat infections

Chronic Glomerulonephritis —Eight cases are in the series (Cases 4 to 11) with six deaths and five necropsies These cases show elevation of blood pressure, marked reduction in phenolsulphonephthalein excretion, very high blood urea or nonprotein nitrogen, fixation of the specific gravity of the urine and usually an albuminuric retinitis

Certain features deserve comment The frequency of either abdominal or lumbar pain, dull and aching in character, as one of the first symptoms observed in these cases is quite striking and has not, we believe, been sufficiently emphasized The reduction in the plasma bicarbonates has been noted before by us[5] as a practically constant feature of this type of nephritis in the final stage In Case 5 a considerable elevation of the plasma bicarbonates was secured by persistent alkaline therapy, but without any beneficial effect on the patient, as far as could be determined It seems probable that the acidosis is without any serious effect per se on the patient, certainly, at least, any deleterious effect it may have is so overshadowed by graver disturbances as to be scarcely recognizable

Of special interest are the kidneys with respect to the plasma chlorids in these patients In contradistinction to the tendency in acute

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3 McLean, F C, and Van Slyke, D D A Method for the Determination of Chlorids in Small Amounts of Body Fluids Jour Biol Chem, 1915, **21,** 361

4 Van Slyke, D D A Method for the Determination of Carbon Dioxid and Carbonates in Solution Jour Biol Chem, 1917, **30,** 347

5 Austin, J H, and Jonas, L Chemical Studies of Acidosis Am Jour Med Sc, 1917, **153,** 81

glomerulonephritis, and indeed, in practically all the other forms of renal disease which we have thus far studied, the plasma chlorids are found to be low rather than high Cases 4 and 10 are within normal limits Case 6 showed a very low figure Whether the venesection and introduction of normal saline intravenously twelve hours before may have influenced this latter reading we are not prepared to say, but it cannot, we feel sure, wholly account for the low reading In Case 5, although the first reading was elevated above the normal, the two subsequent readings were normal and the final reading very low The patient had been kept on a salt-free diet, and this may have favored the reduction in the figure for the plasma chlorids, but does not wholly explain it, for in other forms of nephritis, and, as we have shown elsewhere,[6] in the normal dog it is impossible to produce such a reduction in the plasma chlorids by witholding salt with or without the free administration, by mouth, of distilled water It seems fair to conclude, therefore, that in the last stage of glomerulonephritis, when the elevation of blood urea is the highest observed, there is a tendency to an absence of increase or to an actual reduction below normal of the plasma chlorids The blood pressure falls in all cases shortly before death, but we were surprised to find that throughout the series the drop in the systolic and diastolic pressures was proportional, so that the ratio of the diastolic to the systolic pressure remains practically unchanged We would have expected the fall to occur chiefly in the systolic pressure, but this appears not to be the case

The pathology in all these cases is essentially the same, namely, a glomerulonephritis, with marked cellular proliferation in the tufts and with a variable degree of secondary fibrosis No close parallel can be drawn between the clinical findings and the extent to which the secondary fibrosis of the glomeruli has occurred In Cases 10 and 11 this was very marked In Case 7 it has proceeded to only a very slight extent, in Case 9 the glomerular change was less definitely of the proliferative type and was largely one of hyalinization It is interesting to note that this is the one case of the group coming to necropsy which did not show a very high blood pressure All these cases showed more or less sclerosis of the renal vessels and interstitial fibrosis in the medulla and to some extent in the cortex In the latter the fibrosis is always most marked about the obliterated glomeruli, areas in which the tubules belonging to the glomeruli have undergone collapse with atrophy of their epithelium and sometimes with practically complete obliteration

Grossly, in all of these cases the kidney was contracted and usually pale in color

6 Austin, J H, and Jonas, L Effects of Diet on the Plasma Chlorids and Chlorid Excretion in the Dog, Jour Biol Chem, 1918, **33,** 91

These typical cases constitute a well marked group both clinically and in the histology of the kidney, and the condition deserves the specific name of chronic glomerulonephritis, for, although in the final stages there is extensive destruction of those tubules associated with the most diseased glomeruli, this destruction is clearly secondary to the primary disease of the glomeruli There are good grounds for the view that while the elevation of the blood pressure in these cases is related to the primary glomerular disease, the reduction in the phenolsulphonephthalein output, the retention of the nitrogenous substances in the blood and the fixation of the specific gravity of the urine are consequent on the gradual secondary destruction of the tubules McNider's[7] studies of the spontaneous glomerulonephritis of the dog, we believe, support this view Clinically, we have observed repeatedly in these cases the early appearance of hypertension and the gradual development much later of the impaired renal functional tests

Chronic Diffuse Nephritis —In this group, which is substantially a mixed glomerular and tubular nephritis, we have included four cases (12 to 15) which exhibited one or more of the following edema of the face, waxy pallor, large amounts of albumin in the urine, abundant casts of all kinds, doubly refractile lipoids in the urine, and relatively slight elevation of blood pressure Because of the conspicuous presence of some of these features these cases should doubtless be included in the group of conditions variously called parenchymatous nephritis, tubular or degenerative nephritis, nephropathy or nephrosis Careful study of the cases in this group either clinically or as regards the histology of the kidney in the two cases necropsied shows, however, that these cases merge with those of the previous group The blood pressure in all was at some time more or less elevated, and in Case 12 was quite high The albuminuria was in no case greater than in Case 11 of the other group Casts were scanty in some cases and sometimes absent in others, in no case were they more abundant or more varied in character than in Cases 9 and 11 of the other group The phenolsulphonephthalein test was, at least at the earlier examinations, higher in these cases than in the other group, but this is in part a matter of the stage of the case, for in both Cases 14 and 15 the phenolsulphonephthalein became very low before death, and in Case 7 of the other group the phenolsulphonephthalein was quite fair when first seen, two months before death The difference in the elevation of the blood nitrogen in the two groups is one of degree only, and like the phenolsulphonephthalein probably much influenced by the stage of the disease The plasma chlorids, however, in the cases studied, were

7 MacNider, W de B A Pathological Study of the Naturally Acquired Chronic Nephropathy of the Dog Jour Med Research, 1916, **34**, 177

higher than normal instead of normal or low, as in the other group, and from a recent case we know they may persist above normal until death

In the other group it is worth noting, however, that the patient in Case 5, who exhibited eventually such a low plasma chlorid, had a high plasma chlorid when first seen five weeks earlier The urinary specific gravity tends to approach fixation at about 1 011 to 1 013, although this is less pronounced than in the other group In studying the pathology we find no sharp distinction between the two groups in the gross pathology Histologically, it is undoubtedly true that both cases in this group exhibited more evidence of disease or destruction of the tubular epithelium than has occurred in the cases of the other group This was conspicuous, however, only in Case 15 On the other hand, both cases in this group exhibited definite destruction of the glomeruli, in Case 14, indistinguishable in character from that seen in the other group It is true that both cases, and especially Case 15, exhibited less evidence of cellular proliferation in the glomerular tufts than did most of the cases in the other group, the lesions being more in the nature of a hyalinization of the loops This may perhaps be correlated with the lower blood pressure in the cases of this group As regards etiology, it may be noted that Case 5 of the former group and Cases 12 and 15 of this group originated apparently in pregnancy

We conclude, therefore, that these four cases which we have grouped together do not constitute a distinct type of nephritis either clinically or anatomically, but that, owing perhaps to a greater involvement of the tubular epithelium and perhaps to less pronounced cellular proliferation in the glomeruli, they exhibit a somewhat altered picture with a tendency to more edema of the so-called renal type, more albuminuria, a greater abundance and variety of casts, a higher concentration of the plasma chlorids and less increase in the blood urea, less reduction in the phenolsulphonephthalein, less fixation of the urinary specific gravity and less elevation of the blood pressure

We wish to emphasize at this point, however, that the distinctions just named ought not, we believe, be taken as evidence that the excretion of urea and phenolsulphonephthalein is a function of the glomeruli The factors are much too complex to warrant such conclusions from cases that resemble each other so closely as do those of these two groups Moreover, there is good experimental evidence to support the view that the chief excretion of both urea and phenolsulphonephthalein is a function of the tubules This view is supported by the fact that, in the early stages of glomerulonephritis, when the anatomic lesions are in many cases practically confined to the glomeruli, although the blood pressure is elevated, the blood urea and the phenolsulphonephthalein excretions are quite normal Later, in the advanced stages, when the blood urea and the phenolsulphonephthalein are markedly

altered, there is always extensive obliteration of a large number of the renal tubules secondary to the fibrosis and obliteration of their associated glomeruli

We are disposed to apply to such cases as those in the group that includes Cases 12 to 15 the simple term chronic nephritis or chronic diffuse nephritis without further qualification, and to reserve for the typical cases of the former group the more specific term chronic glomerulonephritis

Arteriosclerosis—The series includes nine cases of arteriosclerosis with cardiac decompensation (Cases 16 to 24), four with necropsy The kidneys of these cases varied to a considerable degree Two were grossly of the so-called arteriosclerotic type, one was a small, pale kidney, one was normal grossly Histologically, they showed practically normal glomeruli, little or no change in the tubular epithelium, little interstitial fibrosis, more or less marked sclerosis of the larger arteries and less or none of the smaller vessels, and a more or less marked degree of passive congestion which in Case 18 was very intense The blood pressure in these cases was for the most part a little lower than those seen in the cases of chronic glomerulonephritis, and the ratio of pulse pressure to systolic pressure was lower in this group A fall of blood pressure occurred as death approached, but, as noted in the former group, the fall in pulse pressure was, to our surprise, not greater relatively than is the fall in systolic pressure The phenolsulphonephthalein excretion was moderately good, being over 20 per cent in two hours in all but two cases which were studied about a month before death when cardiac decompensation was quite marked In one case an elimination of 60 per cent was observed Increase in blood urea or nonprotein nitrogen was of very moderate proportions The plasma chlorids were normal or approximately normal in the cases studied The plasma bicarbonates were but little lowered except in one case Urinary specific gravity exhibited about the same range as would be seen in a similar series of normal cases and showed little tendency to fixation

Three additional cases (25 to 27) were also instances of arteriosclerosis, but the presence of edema of the face, headache, vomiting and impaired vision suggested the association, in addition, of more or less chronic nephritis Two of these cases coming to necropsy confirmed this suspicion, since both exhibited, in addition to arteriosclerosis, a rather early stage of chronic glomerulonephritis with cellular proliferation in the tufts The blood pressure and the relative pulse pressure in these cases was higher than in arteriosclerotics and resembled that of the chronic glomerulonephritis group The phenolsulphonephthalein was moderately reduced The blood urea or non-

protein nitrogen exhibited an increase intermediate between the slight increase of the arteriosclerotics and the marked increase of the late glomerulonephritics Plasma chlorids, plasma bicarbonate and urinary specific gravity correspond rather with the observations in the arteriosclerotic group (These cases are presumably instances of what Volhard and Fahr[8] in their recent monograph have called "Kombinationform") In Case 26 the history is inadequate In the other two cases recent infections, pneumonia and acute rheumatism, had occurred and may be considered as probable causes of the nephritis superimposed on the arteriosclerosis

Miscellaneous—Cases 28 and 29 exhibited what we interpret as a somewhat confusing combination of weakened myocardium and chronic diffuse nephritis In the tendency to slight elevation of blood pressure and to edema of face these cases suggest chronic nephritis The renal functional tests, however, indicate strikingly little impairment of renal function

Case 30 exhibits a rather pronounced impairment in certain of the renal functional tests, but at necropsy showed merely a pronounced fatty degeneration of the epithelium of the convoluted tubules It illustrates how marked an impairment of phenolsulphonephthalein excretion and accumulation of waste nitrogen in the blood can result from a purely tubular lesion or occur with no other renal lesion than this

CONCLUSIONS

1 The cases of acute nephritis showed rather a pronounced impairment of all the renal functional tests

2 The cases of advanced chronic glomerulonephritis showed, in the most pronounced degree, elevation of blood pressure, depression of phenolsulphonephthalein excretion, elevation of blood urea or nonprotein blood nitrogen, fixation of urinary specific gravity and the presence of albuminuric retinitis

These cases were characterized, however, by a normal or even a definitely subnormal plasma chlorid level, and by a considerable reduction of the plasma bicarbonates

Those cases which exhibited marked tendency to proliferative changes in the glomerular tufts were characterized, as a rule, by higher blood pressure than the cases which exhibited chiefly hyaline changes in the tufts

3 The cases which might have been classed clinically as chronic parenchymatous nephritis or as nephroses, because of the very slight elevation of blood pressure, the less marked depression of phenolsulphonephthalein, the less marked elevation of nonprotein nitrogen and

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Case	Clinical Diagnosis	Sex	Age	Symptoms of Onset	Anemia	Blood Pressure
L H	Acute septic nephritis, septicemia	♀	36	Sepsis following abortion	Moderate	157- 91 86- 59
C J	Acute postinfectious glomerulonephritis	♂	35	Edema face and feet, oliguria, anorexia	None	155-105 130- 80
J J McF	Early chronic nephritis	♂	24	Edema face, hands and feet, headache, lumbar pain	Slight	145- 90 135- 80
G P	Advanced glomerulonephritis	♂	49	Headache, lumbar pain, edema of face	Moderate	210-145
F G	Advanced glomerulonephritis (pregnancy)	♀	35	Headache, vomiting, dyspnea, edema of feet, impaired vision	Moderate	230-170 140- 90
W M	Advanced glomerulonephritis Terminal infection (?)	♀	38	Oliguria, loss of consciousness, convulsions	Slight	160-100 135- 90
M W	Chronic glomerulonephritis	♀	28	Weakness, vomiting, headache, vertigo, abdominal pain	Marked	260-175 190-120
A C	Arteriosclerosis, chronic glomerulonephritis	♀	61	Headache	Slight	260-135 190-120
J W C	Chronic glomerulonephritis	♂	46	Weakness, tires easily	Moderate	160- 95 140- 85
F K	Advanced glomerulonephritis	♂	34	Headache, vomiting, abdominal pain	Slight	178-115 120- 85
W L	Advanced glomerulonephritis	♂	28	Lumbar pain, vomiting, headache	Moderate	215-130 150- 90
E M	Chronic nephritis (pregnancy)	♀	42	Lumbar pain, impaired vision, headache, edema face and feet eclampsia	None	210-130 200-125
R C	Chronic nephritis	♀	15	Edema face and feet, headache, impaired vision, vomiting	Moderate	140- 95 125- 85
M O	Chronic nephritis	♀	24	Abdominal pain, vomiting, weakness	Moderate	170- 80 145- 75
S G	Chronic nephritis (pregnancy)	♀	20	Edema face, headache impaired vision, vertigo	Marked	165-105 128- 85
J F	Arteriosclerosis, cardiac decompensation	♂	57	Weakness dyspnea	None	180-130 165-110
H R	Arteriosclerosis, cardiac decompensation	♂	69	Edema face and legs, dyspnea, oliguria	Slight	105- 75 98- 75
I S	Arteriosclerosis cardiac decompensation	♂	68	Edema legs, dyspnea, weakness	Slight	150- 95 130- 90
D E	Arteriosclerosis, cerebral hemorrhage	♂	54	Apoplexy	Slight	220-160 145- 95
C S	Arteriosclerosis, cardiac decompensation luetic	♂	38	Dyspnea, weakness, cough, edema legs	None	195-125 170-110
R W	Arteriosclerosis cardiac decompensation, luetic	♂	40	Edema of legs, dyspnea, oliguria	Slight	195-100 135- 75
H J B	Arteriosclerosis cardiac decompensation, emphysema	♂	54	Edema legs, dyspnea	None	175-110
M M	Arteriosclerosis, cardiac decompensation	♀	57	Cough, dyspnea, edema back, legs and face	None	145-100 100- 70
P H	Gastric carcinoma cardiac decompensation	♂	54	Epigastric pain, dyspnea, weakness, edema legs	Severe	123- 65
S P	Arteriosclerosis chronic nephritis cardiac decompensation	♂	50	Edema legs, dyspnea, vomiting, headache	Moderate	240-130 205-110
J M B	Arteriosclerosis, chronic nephritis, cerebral hemorrhage	♂	45	Headache, apoplexy	Slight	260-135 190-120
G M	Arteriosclerosis chronic nephritis	♀	50	Cramps in legs weakness, edema of feet and face headache, impaired vision	None	265-160 160- 90
W W B	Postinfectious myocarditis, early chronic nephritis	♂	36	Dyspnea, cough, edema face	Slight	140- 87 180-125
T F	Chronic nephritis cardiac decompensation	♂	35	Edema feet and face, dyspnea, vomiting, oliguria	Slight	145-105 160- 85 135- 65
I C	Heroin habitue asthenia, gastroenteritis	♂	20	Diarrhea, vomiting, weakness	None	105- 80 95- 60

Phenol-sulphone phthalein	Blood Urea N	Non protein Blood N	Plasma NaCl	Plasma CO_2	Urinary Specific Gravity	Eyegrounds	Termination
0		112–227			1 008–1 011		Pulmonary edema, death
41–60	52–10		6 5–5 9	61 60	1 015–1 018		Improved
50	12		5 5	71	1 015–1 018		Improved
0	102		5 7	49	1 010–1 012	Sclerosis, hemorrhage	Unimproved
0	125–148		6 1–4 9	36 53	1 010–1 012	Albuminuric retinitis	Unimproved
	165		4 6	48			Convulsions, pulmonary edema, death
45–50					1 015–1 033 1 009–1 013	Albuminuric retinitis	Coma, pneumonia, death
10					1 005–1 010	Albuminuric retinitis	Coma, death
2		127			1 012	Normal	Coma, death
Trace	195		5 5–5 6	36	1 009–1 011		Coma, death
9		108–200			1 011–1 013	Albuminuric retinitis	Pericarditis, death (cardiac)
	29		6		1 013–1 015		Improved
33–50	17–23		6 6–6 2	60	1 010–1 017	Fullness of veins	Cardiac failure, death
22–0		78			1 012–1 021 1 010–1 012		Coma, death
22–5		81			1 009–1 020		Oliguria, death (cardiac following decapsulation)
15					1 020–1 021		Cardiac, death
		30			1 018–1 025		Pneumonia, death
13		48			1 020–1 025		Cardiac, jaundiced, death
30		35			1 021		Apoplexy, pulmonary edema, death
35	17		5 6		1 017–1 021		Improved
20	35–17		5 9–5 8	46 53	1 021 1 025 1 007–1 012		Improved
27–35	23–9		5 7–5 5	56 61	1 008–1 012		Improved
60	20		5 9	57	1 005–1 010		Improved
48	29		6 0	66	1 012–1 017		Unimproved
30–16	26–52		5 8–6 3	63 52	1 012–1 022	Albuminuric retinitis	Improved
	58		5 5	61	1 007		Apoplexy, death
21–12		72			1 009–1 020		Coma, Cheyne Stokes, circulatory death
42–32	15–20		5 9–5 5	59 65	1 013–1 027	Normal	Improved
50–60	12–19		6 0–5 7	35 53	1 017–1 021	Normal	Improved
7		55			1 003		Collapse, death

the more nearly normal urinary specific gravity, and because they exhibited conspicuous edema, especially of the face, and abundant albumin and casts of all kinds in the urine — these cases were less definitely characterized histologically than had been expected While it is true that they showed pronounced degenerative or necrotic changes in the tubular epithelium, they also showed conspicuous, even advanced glomerulonephritis Histologically, their separation from the clinical group of advanced glomerulonephritis would have been difficult, perhaps impossible Grossly, the kidneys in these cases were identical with those of the other group just mentioned We prefer to call these cases simply "chronic nephritis" without further qualification

The plasma chlorids were elevated in the two cases of this group studied in this connection

4 The cases which clinically and histologically were cases of renal arteriosclerosis, exhibited a variety of forms of kidney, grossly, and could not have been properly classified on gross appearance alone The blood pressure, and especially the pulse pressure, although much above normal, were usually lower than in cases of advanced glomerulonephritis

The plasma chlorids and plasma bicarbonates were normal or approximately so

5 In all cases with elevation of blood pressure some fall of pressure was noted in the last five or ten days before death Contrary to expectation, however, the fall in diastolic pressure was closely proportional to the fall in systolic pressure, and not less, as would have been expected

PROTOCOLS OF CASES

CASE 1—*Acute Diffuse and Suppurative Nephritis Following a Septic Endometritis with Pyemia*

L H, woman, aged 26, was admitted three weeks before death because of abdominal pain

The patient had had measles in childhood, scarlet fever at 26 For several years she had had attacks of otitis media Two months before death, following a severe nervous shock, she developed a recurrence of otitis media A month before death an abortion was attempted, followed by abdominal pain, diarrhea, a slight fever and a leukocytosis of 18,000 The leukocytosis increased to 55,000, with 88 per cent of polymorphonuclear neutrophils a week before death, and then declined to 28,000 with the same differential percentile count The patient grew progressively weaker, developed acute suppurative parotitis, followed by cellulitis, a progressing anemia and died with pulmonary edema

The phenolsulphonephthalein test showed no excretion during the last two weeks The total nonprotein nitrogen was as follows 16 days before death, 112 mg per cubic centimeter, 14, days, 144 mg , 12 days, 179 mg , 9 days, 227 mg , 7 days, 208 mg , 5 days, 112 mg The fall in blood nitrogen during the last week was associated with the development of persistent vomiting The blood pressure was 118-82 twenty-one days before death and rose to 157-91 fourteen days before death The urine was of good volume to the end, specific

gravity, from 1 008 to 1 014, albumin, from a light cloud to solid, casts regularly absent, pus abundant, erythrocytes usually in considerable numbers

At necropsy there was found septic endometritis, cellulitis and suppurative otitis of the entire right ear, multiple small abscesses in the lungs The kidneys were large, red and flabby Histologically most of the glomeruli exhibited some degree of acute intracapillary glomerulonephritis, in many this was scarcely noticeable, in others it was quite marked and there was desquamation and exudation in Bowman's capsule The tubules exhibited granular degeneration and some contained desquamated epithelium and many erythrocytes There was marked interstitial hyperemia and edema and areas of lymphocytic and polymorphonuclear infiltration that constituted minute abscesses

CASE 2—*Acute Glomerulonephritis with Tubular Involvement, Recovery*

C J, man, aged 35, colored, admitted Sept 26, 1916, because of edema of the feet, legs and scrotum, discharged Nov 27, 1916, improved

The patient had measles in childhood, gonorrhea at 19, used alcohol freely Three weeks before admission he developed feverishness and pains in the extremities Two weeks later he noticed swelling of the feet and face and later of the legs and scrotum, the urine was scanty and reddish, there was loss of appetite

On admission he presented edema as described, slight icterus seen in the sclerae, the heart of normal size, first sound of poor tone, second, slightly accentuated, the urine, 400 to 1,000 c c on admission, rose to 2,000 c c before discharge, the specific gravity was from 1 015 to 1 018, albumin, at first, almost solid, later reduced to traces, at first, abundant hyaline, granular and leukocytic casts, a few erythrocytes, many leukocytes and renal epithelium, on discharge no casts, leukocytes and epithelium about normal, still a few erythrocytes The blood pressure fell from 155-105 to 130-80 The blood count was normal, the Wassermann, negative

	Phenolsulphonephthalein	Blood Urea N	Plasma Chlorids	Plasma CO_2
Admission	41	52	6 5	61
Discharge	60	10	5 9	60

The patient was kept on a salt-free, low protein diet, with limited fluid intake He was discharged free of edema, having lost 40 pounds

CASE 3—*Early Chronic Glomerulonephritis*

J J McF, man, aged 24, was admitted Dec 28, 1916, because of weakness, headache, and lumbar pain

The patient had had typhoid at 12, pneumonia at 14, was subject to colds and sore throat and had a chronic cold A year before admission he had a sudden attack of edema of the face, later of legs and hands He was admitted to a hospital with blood pressure of 220 and kept in the hospital four months His urine had since continued to show evidences of nephritis Eight weeks before admission here, following a chilling, he developed headache, chills and lumbar pains These persisted or increased until admission He had formerly been a heavy drinker, teeth very poor, with much pyorrhea Enlarged post cervical glands, heart slightly enlarged, sounds normal The urine was 100 to 200 c c in amount, specific gravity from 1 015 to 1 018, albumin, from a cloud to a trace, casts, hyaline and granular, sometimes many, sometimes very few The blood pressure ranged from 145-90 to 135-80 The blood showed a slight anemia, Wassermann negative

CASE 4—*Advanced Glomerulonephritis*

G P, man, aged 49, was admitted Oct 11, 1916, for headache and lumbar pain

The patient had had no previous illnesses, had always been a heavy eater of meat, had taken four or five glasses of beer daily, a heavy tea drinker and

moderate user of tobacco The symptoms began about seven months before admission as attacks of severe pain in the back of the neck, followed by headache and vertigo, frequently dull lumbar pain, slight puffiness about the eyes

On admission the patient was pallid, had enlarged posterior cervical lymph nodes, heart slightly enlarged, slight aortic systolic murmur, greatly accentuated second aortic sound The urine was normal in amount, specific gravity from 1 010 to 1 012, albumin, a cloud, occasional granular casts, increased leukocytes The blood pressure was 210-145 The blood count showed a moderate anemia The eyegrounds showed sclerotic vessels, a small hemorrhage, areas of fatty degeneration, but not typical albuminuric retinitis

CASE 5—*Advanced Glomerulonephritis*

J G, woman, aged 35, was admitted Nov 14, 1916, for dyspnea, discharged Dec 27, 1916, not improved

The patient had had measles, mumps and whooping cough in childhood Four years before admission she was delivered of a 7 months' dead child following a threatened eclampsia with impaired vision, thereafter, subject to severe headaches, sometimes with vomiting She had a light case of scarlet fever two years before admission Two months before admission she noticed dyspnea worse at night, progressive impairment of vision and slight edema of the feet

On admission the heart was enlarged, systolic mitral murmur, accentuated second sound, slightly enlarged liver, little or no edma The urine was normal in amount, specific gravity from 1 010 to 1 012, albumin, a heavy cloud, no casts, a slight increase of leukocytes The blood pressure ranged from 230-170 to 140-90 The blood showed a moderate anemia, the Wassermann was negative The eyegrounds showed sclerosis, hemorrhages, exudates and blurring of the margins of the disks She was kept on a low protein, salt-free diet with 3 gm each of sodium citrate and sodium bicarbonate per day

Date	Phenolsulphonephthalein	Blood Urea N	Plasma Chlorids	Plasma CO_2
11/15	0	125	6 1	36
11/24	—	145	5 5	44
12/ 1	—	148	5 4	53
12/20	—	127	4 9	53

Dec 20, 1917, she had two convulsions, following which 20 ounces of blood were removed, the functional study of which date was made twelve hours later

CASE 6—*Advanced Glomerulonephritis Terminal Infection (?)*

W M, woman, aged 38, was admitted six days before death for unconsciousness and convulsions

The patient had had smallpox at 6, for twenty years she had had lumbar pain, worse the last six years, had been a free drinker of beer Two years previously she had had diphtheria Five months prior to admission she had had a supravaginal hysterectomy for carcinoma of the fundus, followed by radium treatments For a few days before admission the patient had noticed progressive oliguria During the twelve hours before admission she was unconscious, with three convulsions The heart was slightly enlarged, a mitral systolic murmur was present There was almost complete anuria, 10 c c of urine obtained by catheter was bloody and contained a light cloud of albumin, no casts, many erythrocytes, and was loaded with leukocytes The blood pressure ranged from 160-100 to 135-90 The blood showed a slight anemia, a leukocytosis of 23,000 with 91 per cent polymorphonuclear neutrophils, Wassermann negative Lumbar puncture gave normal fluid She had a temperature of 104 F a few hours before admission, falling then below normal, to rise in the last twelve hours to 102 She had repeated convulsions until death ensued, with pulmonary edema Necropsy was refused

	Blood Urea N	Plasma Chlorids	Plasma CO_2
Five days before death	185	4 6	48

This study was made twelve hours after a venesection of 300 c c, with introduction of 240 c c of physiologic sodium chlorid solution

CASE 7—*Chronic Glomerulonephritis*

M W, woman, aged 28, colored, admitted two months before death complaining of vomiting, pain in the stomach and headache

The patient had had measles as a child, frequent attacks of indigestion, with distention Four years before she had had rheumatic fever For three years she had had pain and tenderness in the left hypochondrium, worse after eating, later, vomiting became associated with these attacks Severe headaches were frequent and associated with vertigo and weakness

On admission the tonsils were found to be enlarged, the heart enlarged to both right and left, especially the latter, with accentuated second aortic sound The urine was normal in amount During the first two weeks the specific gravity ranged from 1 005 to 1 033, subsequently it remained from 1 009 to 1 013 Albumin was present in traces or moderate clouds Casts were sometimes absent, sometimes occasional hyaline or granular casts were seen Five weeks before death she had an attack of severe left-sided abdominal pain, with nausea, the left kidney became palpable and cystoscopic examination revealed only a little bloody urine coming from the left ureter The blood pressure ranged from 260-175 to 200-125 until three days before her death, when it fell to 190-120 The phenolsulphonephthalein excretion sixty days before death was 45 per cent for two hours, forty-six days before death, 10 per cent , twenty-one days before death, 10 per cent , sixteen days before death, 5 per cent Forty days before death there was no elimination of indigo-carmin in thirty minutes The eyegrounds two months before death showed extensive arteriosclerosis of the retinal vessels, with numerous exudates about the posterior pole Two weeks later the eyegrounds showed fresh exudates The blood count, normal two months before death, fell to 30 per cent of hemoglobin and 2,200,000 red blood cells two weeks before death During the last week the patient was stuporous and vomited persistently The lobar pneumonia found at necropsy was unrecognized during life and gave no rise of temperature and no notable increase in the already pronounced dyspnea For the last month considerable edema of the legs was present and also hydrothorax, hydropericardium and ascites The Wassermann was negative

At necropsy there was found lobar pneumonia of the right lower lobe, hydrothorax, hydropericardium, ascites, a healed tuberculous lesion at the left apex, caseous bronchial lymph nodes, cloudy swelling and fatty degeneration of the liver The kidneys were about normal in size, pale, with cysts In the lower pole of the left kidney was a large hemorrhagic infarct showing at its edges beginning organization, this was doubtless the cause of the pain and hematuria five weeks before death

Histologically an occasional glomerulus was fibrous and obliterated, but almost all showed little change, there was slight cellular proliferation in the tufts The tubules were for the most part somewhat dilated, with flattening of the epithelium and some granular degeneration There was rather marked diffuse increase of the interstitial fibrous tissue throughout the cortex, and, to a much less marked degree, in the medulla The smaller vessels showed thickened walls Throughout there was moderate congestion

CASE 8—*Arteriosclerosis and Chronic Glomerulonephritis*

A C, woman, aged 61, was admitted fifteen days before death because of headache

There was a previous history of discharging ears for some years and frequent attacks of severe headache Six weeks before death the patient became suddenly unconscious, recovered in a few days but remained confused, weak, with severe headache, defective vision, palpitation and polyuria

On admission there was slight edema of the ankles, the heart was enlarged both to the right and left, with mitral and aortic systolic murmurs The urine was abundant, specific gravity from 1 005 to 1 010, albumin, a cloud, casts varying from none to many granular The blood pressure ranged from 240-150 to 150-100 shortly before death The phenolsulphonephthalein excretion twelve days before death was 10 per cent for two hours Both eyegrounds showed an albuminuric retinitis with exudates, hemorrhages and sclerosis Death occurred in coma

The kidneys histologically showed almost half their glomeruli obliterated by fibrosis, the remainder exhibited marked cellular proliferation and round cell infiltration, the remaining tubules showed slight granular degeneration and the lumina contained a little precipitated albumin There was marked fibrosis of the medulla The vessels had greatly thickened, sclerotic walls

CASE 9—*Chronic Glomerulonephritis*

J W C, man, aged 46, a typesetter, exposed to lead, admitted eighteen days before death for weakness and a tendency to tire quickly

No infections in childhood were recalled He began work as a typesetter at 16 Since the age of 21 he had been subject to occasional epileptiform attacks, more frequent recently At 39 he had an attack of acute articular rheumatism lasting three months, had slight indigestion for several years A month before death he noticed that he tired easily and his legs felt heavy

On admission he was observed to be a pallid, slightly sclerotic individual, heart moderately enlarged, with mitral and aortic systolic murmurs, the liver a trifle enlarged The urine was normal in volume, specific gravity persistently 1 012, albumin, a moderate cloud, abundant hyaline, granular and epithelial casts The blood pressure ranged from 160-95 to 140-85 The eyegrounds were normal The Wassermann was negative The blood showed hemoglobin 40 per cent, red blood cells, 3,000,000, no signs of basic degeneration No lead line was present, nor was there any neuritis A terminal pericarditis and pleuritis developed and he succumbed, with pulmonary edema

Only partial necropsy was permitted The kidneys were pale, granular and contracted Histologically the glomeruli exhibited all stages of destruction by fibrosis and hyalinization of the tufts A few were completely obliterated All showed destruction of one or more capillary loops The capsules were thickened All of the tubules were more or less encroached on by interstitial hyperplasia The tubular epithelium exhibited flattening and atrophy and a moderate granular degeneration and the lumina of many were dilated and contained albumin and casts In one area the capsular spaces of four glomeruli and the lumina of the associated tubules were filled with blood The medulla showed extensive fibrosis, with distortion of the tubules Vascular sclerosis was slight

CASE 10—*Advanced Chronic Glomerulonephritis*

F K, man, aged 34, a paper hanger, admitted three weeks before death for weakness and vomiting

The patient had had the more trivial infections of childhood, repeated attacks of quinsy, had had a chronic suppurative otitis media for twenty-five years, gonorrhea at 19 A year before death the patient began to have attacks of headache, with vomiting, at times with abdominal pain and cramps in his legs Seven weeks before death he began to suffer with dyspnea, cough and a sense of smothering

On admission he was pallid, moderately sclerotic, teeth in very bad condition, heart enlarged both right and left, with a mitral regurgitant murmur and accentuated second sounds The Wassermann was negative There was a slight anemia The urine was of normal volume, specific gravity from 1 009 to 1 011, albumin from a trace to a moderate cloud, casts, sometimes many hyaline and granular, sometimes none The blood pressure, 178-115, fell before death to 120-85 The phenolsulphonephthalein, two weeks before death, was only a trace The blood urea nitrogen, ten days before death, was 195 mg

per 100 c c , the plasma chlorids from 5 5 to 5 6 gm per liter, the plasma bicarbonate, 36 volumes per cent

Only partial necropsy was permitted The kidneys were small, granular and contracted Histologically about half to two thirds of the glomeruli were wholly fibrous and obliterated and these appeared to be grouped in certain areas Here the tubules were collapsed, atrophic and almost obliterated by the interstitial hyperplasia and round cell infiltration In other areas the glomeruli showed no fibrous hyalinization or thickening of the capsules, but did exhibit a cellular proliferation in the tufts In these areas the tubules were more nearly normal and showed only a slight granular degeneration of the epithelium, with albumin and casts in the lumina The medulla showed a rather cellular interstitial hyperplasia of moderate grade The vessels exhibited a marked sclerosis The glomerulonephritis was apparently very advanced in certain areas, while in intermediate zones it appeared to be comparatively early

CASE 11 —*Advanced Chronic Glomerulonephritis*

W L, man, aged 28, was admitted five weeks before death because of vomiting, headache and impaired vision

The patient had had chickenpox in childhood, five years before death he had had gonorrhea, about the same time he had had sudden attacks of lumbar pain and was told at that time that he had Bright's disease Two months before admission he began to have attacks of vomiting associated with severe frontal headache A month later his vision became seriously impaired

On admission he was pallid, had a slight adenopathy, beaded, sclerotic arteries, tonsils enlarged and the right tonsil ulcerated and infected with the characteristic organisms of Vincent's angina, the heart was enlarged to the right and left, with short, inconspicuous systolic and diastolic murmurs at both apex and base The urine varied in amount from 800 to 2,000 c c , the specific gravity fixed from 1 011 to 1 013, albumin, about 2 5 gm per liter (Esbach), many hyaline, light and dark granular casts, leukocytes somewhat in excess of normal, a few doubly refractile lipoids The blood pressure ranged from 215-130 on admission to 150-90 the day before his death The phenolsulphonephthalein excretion on admission was 9 per cent for two hours The total nonprotein blood nitrogen was from 118 to 108 mg per 100 c c soon after admission, and 200 mg three weeks before death The eyegrounds on admission showed a neuroretinitis, with marked exudates and flame-shaped hemorrhages The blood count was persistently about 60 per cent of hemoglobin, red blood cells, 2,700,000 The Wassermann was negative Three weeks before death dyspnea became intense and edema of the legs and enlargement of the liver developed A week before death a pericardial friction appeared He succumbed from circulatory weakness

At necropsy the heart was hypertrophied, the aortic valves sclerotic, bilateral hydrothorax, passive congestion of all the viscera, with some fibrosis The kidneys were small, pale, capsule adherent, surface finely granular and studded with several small cysts Histologically three fourths of the glomeruli were wholly fibrous and obliterated, the remainder showed marked cellular proliferation in the tufts and some thickening of the capsules The tubules around the obliterated glomeruli were collapsed, with atrophied epithelium, and were almost obliterated by the marked cellular interstitial hyperplasia and round cell infiltration The tubules near the intact glomeruli were somewhat distended and showed a moderate granular degeneration and some flattening of their epithelium, their lumina contained precipitated albumin The medulla showed a marked cellular interstitial proliferation and considerable congestion There was marked thickening of the vessel walls

CASE 12 —*Chronic Diffuse Nephritis*

E M , woman, aged 42, was admitted Nov 1, 1916, for backache, impaired vision, edema of the face and legs, discharged Nov 13, 1916, improved

The patient had had measles and diphtheria in childhood, pneumonia at 35 During her third pregnancy, March to December, 1914, the patient suffered from pain in the lumbar region, and after delivery vision was impaired and she fatigued readily During her fourth pregnancy, October, 1915, to June, 1916, she had albuminuria, edema of the feet and one convulsion, after delivery a second convulsion, edema of the feet and face and severe headaches, subject to colds and coughs

On admission the heart was enlarged, second sound accentuated, slight edema of the legs The urine was normal in amount, specific gravity from

TABLE 2—

Case No	Gross Ap pearance	Glomular In volvement	Tubular De-generation	Tubular Di latation	Fibrosis Cortex
1	Large red	Acute	Granular	None	Abscesses
7	Small white	Early chronic (proliferative)	Atrophy, granular	Moderate	Marked
8		Intermediate chronic (proliferative?)	Granular	None	None
9	Small white	Intermediate chronic (hyaline?)	Atrophic, granular	Moderate	Marked
10	Small	Advanced chronic (proliferative)	Slight granular	None	Only around ob literated glomeruli
11	Small white	Advanced chronic (proliferative)	Granular	Moderate	Slight except around obliter ated glomeruli
14	Small	Intermediate chronic (Mixed)	Granular fatty	None	Marked
15	Small	Advanced chronic (hyaline)	Atrophic, marked desquamation	Moderate	Moderate
16	Normal	None	None	None	None
17	Arteriosclerotic	None	Slight granular	None	None
18	Arteriosclerotic	None	Granular	None	None
19	Small white	None	None	None	None
26	Small red	Early chronic (proliferative)	None	Moderate	Marked
27	Small red	Intermediate chronic (proliferative?)	Slight	Marked	None
30	Large white	None	Fatty	None	None

1 013 to 1 015, albumin, a cloud, a few hyaline casts, many leukocytes The blood pressure ranged from 210-130 to 200-125 The blood count was normal, the Wassermann was negative

CASE 13—*Chronic Diffuse Nephritis*

R C, girl, aged 15, was admitted June 21, 1916, for anasarca, discharged Sept 30, 1916, slightly improved

The patient had had measles and whooping cough in childhood Five months before admission she noticed edema of the feet associated with headache, black spots before the eyes, vomiting, all of gradual onset There was general anasarca with involvement of the face, very pallid, tonsils enlarged and cervical lymph nodes palpable, heart normal in size, sounds, fair, no murmurs, bilateral hydrothorax and ascites The urine ranged from 500 to 1,200 c c in amount, specific gravity, from 1 010 to 1 017, albumin, a heavy cloud, loaded with hyaline,

light and dark granular, epithelial and fatty casts, many leukocytes, abundant, doubly refractile lipoids, free, on casts and in compound granule cells and very large The blood pressure ranged from 140-90 to 125-85 The phenolsulphonephthalein excretion varied from 33 to 50 per cent in two hours after intravenous injection The blood urea nitrogen was from 17 to 23 mg per 100 c c The plasma chlorids 6 2 gm per liter after two months on a salt-free low protein diet, the calculated threshold, 6 05 gm The blood showed a moderate anemia and a persistent, slight leukocytosis of about 13,000 to 20,000 The eyegrounds show the disk anemic; kinking of the arteries and compression of the

—Pathological Data

Fibrosis Medulla	Arteriosclerosis Large	Arteriosclerosis Small	Congestion	Pathological Diagnosis
Cellular	None	None	None	Acute suppurative nephritis, acute glomerulonephritis
Moderate	None	Moderate	Moderate	Early chronic glomerulonephritis, arteriosclerosis
Marked	Marked	Marked	None	Arteriosclerosis, intermediate chronic glomerulonephritis
Marked	Slight	Slight	None	Intermediate chronic glomerulonephritis, arteriosclerosis
Cellular	Marked	Marked	None	Advanced chronic glomerulonephritis, arteriosclerosis
Cellular	Marked	Marked	Moderate	Advanced glomerulonephritis, arteriosclerosis
Marked	Marked	Marked	None	Arteriosclerosis, intermediate chronic glomerulonephritis, marked tubular involvement
Marked	Marked	None	None	Advanced chronic glomerulonephritis, marked tubular involvement, slight arteriosclerosis
Slight	Slight	None	Moderate	Arteriosclerosis, congestion
None	Slight	Slight	Marked	Arteriosclerosis, congestion
Slight	Moderate	Moderate	Intense	Arteriosclerosis, congestion
None	Marked	None	None	Arteriosclerosis
Marked	Marked	Marked	Marked	Arteriosclerosis, early chronic glomerulonephritis
Marked	Intense	Intense	None	Arteriosclerosis, intermediate chronic glomerulonephritis
None	None	None	None	Fatty degeneration

underlying veins, which were unduly full, pigmentation, doubtful evidence of old hemorrhages The Wassermann was negative

The patient died in another hospital Feb 12, 1917, with cardiac symptoms, the death being from cardiac failure Just before death the urine, blood and blood pressure were substantially those given There was no necropsy

Date	Phenolsulphonephthalein	Blood Urea N	Plasma Chlorids	Plasma CO_2
7/ 5	50			
7/17		23	6 6	60
8/ 4	33			
9/ 1		17		
9/ 5	50			
9/16		20	6 2	

CASE 14—*Chronic Diffuse Nephritis*

M O, woman, aged 24, admitted March, 1915, seventeen months before death, for pain in the lower abdomen, vomiting and weakness

No previous illnesses The patient had had occasional abdominal pain since a kick in her left side two years before admission Vomiting and weakness developed just before admission The urine was normal in amount, specific gravity from 1 012 to 1 021, albumin, a heavy cloud, casts, none at times, at others abundant hyaline and light granular casts The blood pressure ranged from 170-80 to 145-75, the phenolsulphonephthalein from 12 to 20 per cent for two hours, the total nonprotein blood nitrogen from 74 to 78 mg per 100 c c The eyegrounds and blood count were normal In November, 1915, in addition she developed edema of the face, headaches, vertigo and occasional diarrhea The breath became urinous The patient seemed somewhat stuporous A moderate anemia was present The urinary specific gravity was persistently 1 011 to 1 012, casts were always abundant The blood pressure ranged from 155-95 to 118-60, the phenolsulphonephthalein excretion from 8 to 22 per cent for two hours, the total nonprotein blood nitrogen was 67 mg per 100 c c After a period of amelioration a return of symptoms with excessive vomiting and headache developed in July, 1916, a week before her death The urinary output was diminished, the specific gravity from 1 010 to 1 012, albumin and casts as before The blood pressure was 150-95, the phenolsulphonephthalein excretion, zero Anemia was marked, hemoglobin, 45 per cent , red blood cells, 2,750,000 The patient died comatose

Only partial necropsy was permitted The kidneys were small, granular, with adherent capsules Histologically about one fourth of the glomeruli were completely obliterated, of the remainder all showed a little intracapillary proliferation and in some, hyalinization of one or more loops had taken place, the capsules were all more or less thickened The tubules were greatly distorted by the marked cortical fibrosis and interstitial round cell infiltration In many of the tubules the epithelium was flattened and atrophic In the remaining tubules the epithelium showed marked fatty, granular degeneration The medulla showed marked interstitial hyperplasia and the tubules for the most part contained casts The vessels showed considerable sclerosis

CASE 15—*Chronic Diffuse Nephritis*

S G, woman, Jewess, aged 20, was first admitted 1913, eighteen months before her death, for swelling of the ankles and face, dyspnea, cough and vertigo

She had had measles, diphtheria and pneumonia as a child Beginning in 1909 she had had asthmatic attacks in damp weather In January, 1912, at the age of 17, when five months pregnant with her only child, she noticed swelling of her ankles, black spots before her eyes and dizziness Following a normal labor in May, 1912, these symptoms subsided, to return in a few months with, in addition, puffiness of the face and headaches

When first seen, July, 1913, the urine showed a specific gravity of from 1 011 to 1 120, albumin 2 to 3 3 gm per liter (Esbach), occasional hyaline and granular casts The blood pressure was 165-105 on admission, falling after rest and treatment to 128-85 There was a slight anemia The eyegrounds were normal The phenolsulphonephthalein test gave an output of 22 per cent in two hours and a month later of 15 per cent In November, 1913, the heart was found somewhat enlarged to the left, paresthesias in the legs had developed Hyaline and granular casts were abundant in the urine The phenolsulphonephthalein excretion had fallen to 10 per cent in two hours The eyegrounds were still normal Two months later she developed a bronchopneumonia which altered the picture but little except for a temporary depression of the blood pressure to 100-50 and a more marked anemia, hemoglobin, 57 per cent , red blood corpuscles, 3,200,000

In December, 1914, five weeks before her death, she was admitted again with symptoms unchanged The blood pressure was 145-110 The urine showed albumin as before, the specific gravity ranged from 1 009 to 1 020, the urine was now loaded with hyaline and granular casts, contained many leukocytes

and many double refractile lipoids The phenolsulphonephthalein elimination was 5 per cent in two hours, the total nonprotein nitrogen, 81 mg per 100 c c The anemia was progressing rapidly and three weeks before death the hemoglobin was 33 per cent, the red blood corpuscles, 2,160,000 Vomiting now became frequent and the urinary output diminished As a last resort decapsulation of the kidneys was performed, January 21 The patient died two days later The Wassermann was negative

Necropsy was refused, but it was permitted to remove the kidneys through the operative incision They were small, pale reddish, with moderately adherent capsule, granular surface and numerous small cysts Histologically the glomeruli were extensively diseased, being partially fibrous and extensively infiltrated with amyloid, the capsules were for the most part thickened, probably two thirds of the glomeruli were wholly obliterated Many of the tubules, especially about the obliterated glomeruli, were collapsed, with atrophied epithelium and surrounded by hyperplastic connective tissue and round cell infiltration The tubules about the glomeruli that were still partially intact showed extensive degeneration and often complete desquamation of the epithelium, and around the basement membranes of many was a moderate amount of amyloid infiltration Most of these tubules contained casts Throughout the cortex there was considerable interstitial fibrous tissue A few of the tubules were distended with blood and others with leukocytes The medulla exhibited a marked hyperplasia of the interstitial tissue, with compression of the tubules The larger vessels showed a considerable degree of sclerosis

CASE 16—*Arteriosclerosis, Cardiac Decompensation*

J F, man, aged 57, was admitted three weeks before death for weakness, dyspnea and dryness of the mouth and throat

This was a case of arteriosclerosis with cardiac decompensation The urine amounted to from 300 to 1,200 c c, specific gravity, from 1 020 to 1 021, albumin, a trace to a cloud, many hyaline and granular casts The blood pressure, 180-130, falling to 165-110 two days before death The blood count was normal, the Wassermann negative The phenolsulphonephthalein excretion on admission was 15 per cent in two hours

At necropsy the kidneys were of normal size and color, the capsule stripped easily, leaving a slight granular surface Histologically the kidney was approximately normal The medulla showed a moderate fibrosis Throughout there was a moderate passive congestion A few of the larger vessels showed thickened walls

CASE 17—*Arteriosclerosis, Cardiac Decompensation*

H R, man, aged 69, was admitted nine days before death because of edema and dyspnea

The patient had had measles and scarlet fever in childhood, chancre in youth Five years before death he developed discharging sinuses about his ankles, which remained open for two years Eight months before death he began to show edema of the face in the morning, and later, of the legs and scrotum Three days before admission he developed dyspnea, rapidly increasing edema and oliguria

On admission the heart was enlarged, sounds feeble, with a mitral systolic murmur A general anasarca was present The urine was diminished in volume, specific gravity, from 1 018 to 1 025, albumin, a trace, at times a few hyaline and granular casts, at others, none The blood pressure ranged from 105-75 to 98-75 The blood urea nitrogen was 30 mg per 100 c c, the plasma chlorids, 5 9 gm per liter, the plasma bicarbonates, 72 volumes per cent The Wassermann was slightly positive He developed a terminal pneumonia five days before death, with a slight transient rise of temperature to 101 3 F, and a leukocytosis of 18,000, of which 93 per cent were polymorphonuclear neutrophils

Only partial necropsy was permitted The kidneys were of almost normal size (135 gm), the capsule was slightly adherent, the surface was red and finely granular Histologically there was pronounced congestion of the glomerular tufts and of the cervical and medullary vessels Precipitated albumin was present in the capsular spaces and lumina of the tubules Otherwise the glomeruli and tubules were approximately normal The tubules exhibited a slight granular degeneration The vessels were but little sclerosed and there was no hyperplasia of the interstitial tissue

CASE 18—*Arteriosclerosis, Cardiac Decompensation*

E S, man, aged 68, was admitted five weeks before death for dyspnea and edema of the legs

He had typhoid in boyhood, scarlet fever at 19 and his kidneys were said to have been affected for some time afterward For three years before death he had moderate edema of the legs, later, with dyspnea and weakness Six weeks before admission there was a brief attack of unconsciousness

He was admitted with enlarged heart, poor cardiac sounds, congestion of the lungs and liver and anasarca The urine was fair in quantity, specific gravity, from 1 020 to 1 025, albumin, a cloud, casts, at times abundant, hyaline and granular, at other times, none The blood pressure was from 150-95 to 130-90 The phenolsulphonephthalein excretion on admission was 13 per cent in two hours At the same time the total nonprotein blood nitrogen was 48 mg per 100 c c There was a slight anemia The patient was jaundiced the last two days of his life Death was from cardiac failure At necropsy there was found marked arteriosclerosis involving especially the coronaries, cardiac hypertrophy and dilatation, recent infarcts in the lung and old infarcts in the kidneys The kidneys were normal in size, hard, dark red, the capsule, slightly adherent, the surface, coarsely granular, one or two small cysts and old infarcts Histologically there was throughout intense passive congestion An occasional glomerulus was fibrosed but the great majority were normal except for the congestion The tubules exhibited some granular degeneration of the epithelium and albuminous precipitate and sometimes a few erythrocytes in the lumina The medulla showed little fibrosis The vessels were moderately sclerotic

CASE 19—*Arteriosclerosis, Cerebral Hemorrhage*

D E, man, aged 54, colored, admitted six days before death because of hemiplegia

This was a case of cerebral hemorrhage occurring the day of admission in an arteriosclerotic with strongly positive Wassermann The urine was of normal quantity, specific gravity, 1 021, a cloud of albumin, abundant hyaline, granular and epithelial casts The blood pressure was 220-160 on admission, falling after venesection to 145-95 The total nonprotein blood nitrogen on admission was 35 mg per 100 cc, the phenolsulphonephthalein excretion two days later was 30 per cent in two hours At necropsy the kidneys were rather small and pale, the capsule stripped with difficulty, leaving a surface almost smooth Histologically the kidney was almost normal Occasionally a fibrosed glomerulus was seen, but the great majority were normal A few showed a slight thickening of the capsule The tubules were in good condition, in a few there was a little albuminous precipitate Some of the larger vessels showed marked sclerotic thickening

CASE 20 —*Arteriosclerotic Hypertension with Cardiac Decompensation Luetic*

C S, man, aged 38, was admitted Oct 9, 1916, for dyspnea, weakness and cough, discharged Oct 25, 1916, improved

A case with strongly positive Wassermann, hypertension, very slight cardiac enlargement, chronic myocarditis and decompensation with slight enlargement of the liver and edema of the legs, blood count normal, the urine normal in amount, specific gravity, from 1 017 to 1 021, albumin a faint trace, a moderate number of hyaline and granular casts, pus The blood pressure was 170-110 to 195-125

CASE 21—*Arteriosclerosis, Cardiac Decompensation, Luetic*

R W, man, aged 40, was admitted Sept 28, 1916, for edema of the trunk and legs, dyspnea and oliguria, discharged Nov 5, 1916, improved

The patient had measles, whooping cough and chickenpox in childhood, two attacks of appendicitis, unoperated, syphilis and gonorrhea at 28, the former treated for four years, used whisky to excess Seven years before admission he began to have attacks of general stiffness, edema of the legs and oliguria, later he became dyspneic on exertion, these attacks had gradually increased in frequency and severity On admission he exhibited intense edema of trunks and legs, pyorrhea alveolaris, congestion of the bases of the lungs, enlarged heart, initial systolic murmur and accentuated second pulmonic sound, palpable, tender liver The urine was diminished in quantity, specific gravity, from 1 021 to 1 025, albumin, a cloud Sometimes many hyaline, granular and occasionally epithelial casts, sometimes none The blood pressure ranged from 135-75 to 195-100, the increase associated with clinical improvement The blood count showed a slight anemia, the Wassermann was negative, eyegrounds were normal except for a slight indentation of the veins

Date	Phenolsulphonephthalein	Blood Urea N	Plasma Chlorids	Plasma CO_2
9/29	20	35	5 9	46
11/ 2		17	5 8	53

The patient on a mixed, salt-free, low protein diet, with cardiac stimulation and fluid intake limited to 500 c c daily, did poorly The oliguria persisted and the edema increased About October 12 he developed diarrhea and mild jaundice He was then placed on a milk diet (1,000 c c daily) and medication withdrawn The diarrhea and jaundice promptly subsided, the urinary output rose to 3,600 c c , specific gravity, from 1 007 to 1 012, and the edema subsided with a loss of weight of 24 pounds in ten days Shortly afterward the second functional studies were made

CASE 22—*Arteriosclerosis, Cardiac Decompensation, Emphysema*

H J B, man, aged 54, was admitted March 23, 1917, for edema of the legs and dyspnea, discharged April 20, 1917, with compensation almost restored

The urine was normal in amount, specific gravity, from 1 008 to 1 012, albumin, a cloud, casts abundant, hyaline, granular and a few leukocytic, later, after restoration of compensation, no casts The blood pressure was about 175-110 The blood count was normal, Wassermann negative

Date	Phenolsulphonephthalein	Blood Urea N	Plasma Chlorids	Plasma CO_2
3/26	27	23		60
4/ 2	29	23	5 7	56
4/20	35	9	5 5	61

The patient was kept on a low protein diet, fluid restricted to from 100 to 1,500 c c , strychnin, digitalis and sodium phosphate were given

CASE 23—*Arteriosclerosis, Cardiac Decompensation*

M M, woman, aged 57, was admitted Sept 12, 1916, because of cough, dyspnea and edema of the back, legs and face, discharged Oct 14, 1916, improved

The patient had had measles and chickenpox in childhood, and was subject to occasional "sore throats" For a year she had had a troublesome cough, dyspnea on exertion, an increased edema of the legs, back and face All the symptoms increased just before admission On admission she presented, in addition, congestion of the pulmonary bases and enlarged heart, with initial systolic murmur and total arrhythmia (auricular fibrillation) The urine was normal in amount, specific gravity, from 1 005 to 1 010, albumin, a faint trace, no casts The blood pressure ranged from 145-100 to 100-70 The phenolsulphonephthalein given intravenously was excreted to 60 per cent in two hours (Sept 17, 1916) The blood count was normal, the Wassermann negative, blood analyses were made Oct 7, 1916

The patient was discharged with edema and dyspnea diminished but not gone, auricular fibrillation persisting She was kept on a salt-free, low protein diet, with limited fluid intake

CASE 24—*Carcinoma of the Stomach, Cardiac Decompensation*

P H, man, aged 54, was admitted Sept 20, 1916, for pain in the epigastrium, discharged Oct 10, 1916, unimproved

This was a case of inoperable carcinoma of the stomach with little or no pyloric obstruction There had been pain of four months' duration and dyspnea, weakness and edema of the legs for the same period, anemia was severe, Wassermann negative, urine normal in amount, specific gravity, from 1 012 to 1 017, albumin, a trace, many hyaline, granular and leukocytic casts The blood pressure was 123-65 Eyegrounds normal, except for pallor

CASE 25—*Arteriosclerosis, Chronic Nephritis, Cardiac Decompensation*

S P, man, aged 50, was admitted June 19, 1916, for headache and edema of the feet, discharged July 17, 1916, readmitted Dec 5, 1916, discharged March 16, 1917, improved

The patient had had acute articular rheumatism at 15 and at 40 Since October, 1915, he had been more or less constantly in hospitals for edema of his legs, dyspnea and occasional attacks of vomiting In April, 1916, he had pneumonia On admission, considerable edema of the legs, heart slightly enlarged, vessels sclerotic The urine was normal in amount, specific gravity, from 1 012 to 1 022, albumin, a heavy cloud, casts, sometimes none, sometimes many hyaline and granular The blood pressure ranged from 240-130 to 205-110 The blood showed a slight to moderate anemia, Wassermann negative The eyegrounds on June 20, 1916, showed sclerosis and hemorrhages, but no exudate or neuritis, on Dec 8, 1916, in addition, the disk margins were hazy and a few exudates were seen

Date	Phenolsulphone-phthalein	Blood Urea N	Plasma Chlorids	Plasma CO_2
6/21/16	30	26	5 8	63
12/ 6/16	18	52	6 3	52
2/12/17	16			

CASE 26—*Arteriosclerosis, Chronic Nephritis, Cerebral Hemorrhage*

J M B, man, aged 45, colored, admitted four days before death because of sudden loss of consciousness

The patient had been subject to headaches and under treatment for Bright's disease for some time He suddenly fell unconscious on the day of admission, exhibited a right-sided hemiplegia, Cheyne-Stokes respiration, heart enlarged to right and left, mitral systolic murmur, marked edema of legs The urine was fair in quantity, specific gravity, 1 007, albumin, a heavy cloud, many hyaline, light and dark granular casts The blood pressure ranged from 260-135 to 235-130 except after venesection, when it fell to 190-120 The blood urea nitrogen was 58 mg per 100 c c, the plasma chlorids, 5 5 gm per liter, the plasma bicarbonates, 61 volumes per cent The blood showed a slight anemia, a leukocytosis of 15,000 with 86 per cent polymorphonuclear neutrophils The Wassermann was negative

At necropsy there was left sided cerebral hemorrhage, a terminal, very recent pneumonia The kidneys were small, red, and granular Histologically there was marked congestion throughout None of the glomeruli were obliterated but most showed moderate cellular proliferation in the tufts and a few, hyalinization of some of the loops, in a few there was a slight thickening of the capsule The tubules appeared somewhat dilated, with fairly preserved epithelium, in the lumina of many were found albuminous precipitate and casts The interstitial tissue in both cortex and medulla was considerably increased The vessel walls were thickened

CASE 27—*Arteriosclerosis, Chronic Nephritis*

G M, woman, aged 50, was first admitted two years before death for general weakness, pains in the legs, edema of the feet and headache

The patient had had measles, pertussis and chickenpox in childhood, malaria for three years at 20, at 25, an acute arthritis of the right knee and transient disturbance of vision, two years later, appendicitis, operated on; pneumonia at 41 and 44 Soon after this she was injured in a trolley accident, three ribs were broken and repeated small hemorrhages from the bowels occurred For a year before admission she had cramplike pains in the legs and general weakness, slight edema of the feet and puffiness of the face in the morning, morning headaches, dyspnea on exertion, spots before the eyes and diplopia The urine was of normal quantity, specific gravity, from 1 011 to 1 017, albumin, a trace to a cloud, casts, none or occasional granular casts The urine was the same two years later, just before death The blood pressure ranged from 180-110 to 265-160 until two days before death, when it fell to 160-90 The phenolsulphonephthalein two years before death was 21 per cent The total nonprotein nitrogen a week before death was 72 mg per 100 c c The eyegrounds two years before death were normal, both eyes showed cataract The Wassermann was delayed negative A week before death the patient became suddenly confused, very weak, with intense headache, dizziness and twitching of the hands Respiration became Cheyne-Stokes in type and the circulation rapidly failed

At necropsy there was marked arteriosclerosis and moderate cardiac hypertrophy The kidneys were very small, red, with very slightly adherent capsule and coarsely granular surface Histologically, the kidney presented a patchy appearance In some areas the glomeruli were completely fibrosed and the neighboring tubules collapsed and practically obliterated by fibrous tissue and round cell infiltration In other areas the glomeruli exhibited moderate cellular proliferation in the tufts, a very little hyalinization of the loops and more or less thickening of the capsules The neighboring tubules showed for the most part greatly distended lumina, the epithelium was fairly well preserved A little albuminous precipitate was present in most of the lumina In these areas there was little interstitial hyperplasia The medulla exhibited marked fibrosis, with considerable distention of the lumina of the tubules The vessels showed intense sclerosis

CASE 28—*Postinfectious Myocarditis, Early Chronic Nephritis*

W W B, man, aged 36, was admitted Feb 27, 1917, for dyspnea, cough and insomnia, discharged April 8, 1917, improved

The patient had had measles, mumps and whooping cough in childhood, typhoid fever at 24 For three months he had had slight dyspepsia, with occasional vomiting after eating Two months before admission he had an attack of grip This was followed in a few days by dyspnea, cough, sleeplessness and palpitation on exertion The day before admission he noticed puffiness of his face The patient was pallid, lungs emphysematous, heart enlarged, with accentuated second sounds, and slight edema of legs and feet The urine was a low normal in quantity, specific gravity, from 1 013 to 1 027, albumin, a trace to a cloud, casts, hyaline, sometimes many, sometimes none The blood pressure gradually rose from 140-87 to 180-125 The blood showed a slight anemia, the Wassermann was negative The eyegrounds showed some unevenness of the caliber of the vessels, otherwise normal While under observation the blood pressure rose, but the circulation and urine improved, the dyspnea and edema disappeared and the weight diminished 35 pounds

Date	Phenolsulphonephthalein	Blood Urea N	Plasma Chlorids	Plasma CO_2
2/28	42	15	5 9	59
3/21	32			
4/ 2		20	5 5	65

The phenolsulphonephthalein on March 21 was estimated just at the end of a week out of the hospital when all the symptoms were exaggerated

Case 29—*Chronic Nephritis, Cardiac Decompensation*

F F, man, aged 35, was admitted Nov 6, 1913, because of edema of legs, palpitation, dyspnea and scanty urine

The patient had had diphtheria at 9, lead poisoning at 26, typhoid at 27, always subject to colds, had had psoriasis for several years, a moderate daily user of alcohol Two years before admission he acquired a severe cold on a fishing trip This was followed by edema of the face and legs, dyspnea, nausea and vomiting and oliguria, lasting a month The present attack was similar and also followed a fishing trip, it was characterized, in addition, by aching in the lumbar region and moderate diarrhea On admission he showed a trace of jaundice in the sclerae, marked edema of the legs, badly kept teeth, heart enlarged, a mitral and a basal systolic murmur The urine ranged from 1,500 to 3,500 c c, specific gravity, from 1 011 to 1 023, albumin, a trace to none, casts, from many hyaline and granular to an occasional hyaline The blood pressure ranged from 145-105 to 132-75 The phenolsulphonephthalein excretion was 50 per cent The patient lost his edema and 20 pounds in weight in two weeks He was readmitted Sept 18, 1916, with the same symptoms, also following a fishing party

The blood showed a slight anemia, Wassermann negative The eyegrounds were normal The urine was from 300 to 1,800 c c, specific gravity from 1 017 to 1 021, albumin and casts as before, the blood pressure 160-85 to 135-65

Date	Phenolsulphone-phthalein	Blood Urea N	Plasma Chlorids	Plasma CO
9/21	50	12	6 0	35
	60	19	5 7	53

During three weeks in the hospital on a salt-free diet, with limited fluid intake, he lost the edema and dyspnea and dropped 30 pounds in weight A fall in the plasma chlorids is to be noted

Case 30—*Heroin Habitué, Asthenia, Gastro-Enteritis*

L C, man, aged 20, was admitted seven months before his death with diarrhea

The patient had had no previous illness For at least five months before admission he had been a heroin habitue For one month he had had diarrhea, nausea, vomiting and intense weakness

When first seen he had lost 30 pounds in weight, had sclerosed and beaded arteries, a liver slightly enlarged, at times slight edema of the feet The feces were often frothy, yellowish with much mucus and an abundance of fat, all the duodenal ferments were present The Wassermann was negative His blood pressure during the last six months gradually fell from 105-80 to 95-60 His phenolsulphonephthalein output five days before death was 7 per cent for two hours and his total nonprotein blood nitrogen 55 mg per 100 c c He exhibited a terminal polyuria (4,800 c c) with a specific gravity of 1 003, albumin, none or a faint trace Six months before death he showed no casts, but during the last two weeks hyaline and granular casts were found The blood was normal, Wassermann, delayed negative He died with symptoms of collapse

At necropsy there was found fibrosis of the spleen and pancreas and hypoplasia of the aorta heart, adrenals and pancreas

The kidneys were large, pale and flabby, with the capsule adherent at certain points The pyramids were dark purple Histologically the glomeruli were normal The epithelial cells of the tubules, especially the proximal convoluted tubules showed marked fatty degeneration or infiltration, the majority appearing as "seal-ring" cells

THE RELATIONSHIP OF THE SO-CALLED IDIOPATHIC CARDIOPATHY TO EXOPHTHALMIC GOITER

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Exophthalmic goiter is usually regarded as a disease dependent on increased or perverted secretion of the thyroid gland This conception is supported by several facts, among them, that partial removal of the enlarged thyroid not uncommonly serves to mitigate the severity of symptoms, while the administration of thyroid extract intensifies those symptoms which are already present or brings out fresh disturbances of various sorts Confirmation is also to be had in the fact that the prolonged administration of thyroid extract to dogs and monkeys results in exophthalmos, increased rapidity of the pulse, changes in nitrogenous metabolism, loss of weight and sweating However true this may be, there are equally good reasons for the belief that alterations in the activity of the thyroid gland are not wholly responsible for the multiplicity of symptoms in exophthalmic goiter, but that other influences are active, such as disturbances in the sympathetic system and, possibly, in the lymphoid tissues, particularly the thymus gland, which, in a certain number of cases of exophthalmic goiter is persistent and apparently flourishing at an age when complete or partial involution is to be expected

The cardinal symptoms of exophthalmic goiter consist in exophthalmus, tachycardia, tremor and enlargement of the thyroid gland, and recognition of the fully developed picture is often accomplished at a glance At other times, however, the signs are less obvious and the diagnosis is correspondingly difficult In this connection the so-called thyroid cardiopathy assumes a place of importance There are two recognized clinical varieties first, a cardiopathy due to mechanical interference by the enlarged thyroid, and second, the thyrotoxic heart The first variety depends on projection of the enlarged thyroid through the upper aperture of the thorax, or on interference with the venous return from the head and neck, and thyroid intoxication, if it enter into the process at all, is sequential and not causative The thyrotoxic cardiopathy, on the contrary, is regarded as a direct result of disturbances in the thyroid secretion, and, according to some clinicians,

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the symptoms associated with it constitute an affection independent of exophthalmic goiter, while others look on them as manifestations of an incompletely developed Graves' disease

According to Kraus, His and others, the thyrotoxic heart gives rise to two groups of symptoms In one group the heart beat is increased in frequency, with or without subjective symptoms of palpitation The pulse varies between 90 and 120 beats to the minute The carotid pulse sometimes throbs visibly and the patient complains of shortness of breath Bilateral exophthalmos is seen, but is not common Unilateral exophthalmos is said to occur rather more frequently, and is associated with pressure of the enlarged thyroid on the corresponding sympathetic ganglion, the pupil is relatively fixed and dilated, and there are inequalities in the temperature of the two sides of the neck A fine tremor of the fingers may be present In a second group of cases, in addition to the symptoms just enumerated, the heart shows signs of enlargement

The cardiopathy of thyrotoxic origin is purely a clinical concept As far as I have been able to learn, the underlying anatomic changes in the heart and in the thyroid gland have never been determined In this connection it is to be recalled that pathologic anatomists have long recognized the existence of a lesion characterized by massive enlargement of the heart occurring without valvular or pericardial, arterial, pulmonary or renal changes to account for it — the so-called idiopathic cardiopathy Six such cases have been encountered in the necropsy room at Bellevue Hospital, and all of them showed naked eye changes in the thyroid gland In five cases the thyroid was considerably enlarged, and in one case it was diminished in size Microscopic examination of the thyroid in five of the cases showed the changes incidental to chronic interstitial inflammation with hyperplasia of the colloid vesicles The sixth could not be examined microscopically Papillary projections into the alveoli were not found The colloid content varied in quantity and in its staining reactions In certain vesicles it was abundant and stained bright red, in others it was pale In no instance was the size or position of the thyroid such as to interfere mechanically with the action of the heart

All of the cases were in adult males, the ages being, respectively, 49, 50, 29, 52, 26 and 34 years The patients were admitted to the hospital with well marked signs of broken compensation in the form of dyspnea and swelling of the lower extremities, the edema sometimes involving the thighs, penis and scrotum The serous cavities frequently were partially obliterated by collections of fluid Cough, cyanosis and precordial pain occurred as occasional incidents With one exception, all of the patients were well nourished Physical

examination showed great increase in the size of the heart, with or without the association of murmurs The radial pulse was at times rapid and irregular, at other times slow, having been counted as low as 40 beats to the minute and as high as 160 in the same patient In two instances in which the blood pressure was recorded the reading was within normal limits, and in all of the cases the artery was described as soft or compressible In none of the cases were all of the cardinal symptoms of exophthalmic goiter detected In two cases, however, there was marked bilateral exophthalmos and, in one of these, there was slight swelling of the neck in the region of the thyroid gland, so that only tremor was lacking to complete the picture At necropsy, five of the subjects showed great enlargement of the heart, and in one instance the heart was described as only slightly enlarged In five cases the enlargement was due to dilatation and hypertrophy of the several chambers without valvular or pericardial, arterial, pulmonary or renal changes to explain the increase in size In one case all of the chambers of the heart were dilated and hypertrophied, with the exception of the left auricle, in a second case both auricles were dilated and both ventricles were dilated and hypertrophied, in a third case the right auricle and ventricle were both dilated and hypertrophied, but the left side of the heart was apparently unchanged, in a fourth case both ventricles and the right auricle were dilated and hypertrophied, in a fifth case the right auricle was dilated and both ventricles were dilated and hypertrophied, and, in the remaining case, the right auricle was dilated and both ventricles were dilated and hypertrophied, but in this instance the changes in the left heart were apparently due to valvular lesions, while those of the opposite side could not be accounted for except as part of a thyroid cardiopathy In four of the cases the endocardium, particularly in the left ventricle, but also in the right ventricle and, occasionally, in the auricles, was diffusely opaque, at other times thickening occurred in patches In two instances the thickened endocardium extended into the underlying heart muscle for a distance of 2 or 3 mm, and in one case the interventricular septum was the seat of numerous small grayish streaks and patches In two cases the apex of the left ventricle showed grayish-red, firmly attached mural thrombi, and, in addition, there were thrombotic infarctions in the lungs and kidneys, a third case was marked by thrombosis of the left ventricle near the apex and by hemorrhagic infarctions in the lungs, two of the subjects showed definite anatomic changes incident to syphilis, one subject showed the changes characteristic of well developed status lymphaticus, in one subject the signs of recessive status lymphaticus were present, and, in a third, the thymus was large and fleshlike in appearance, but other indications of status lymphaticus were lacking

REPORT OF CASES

The clinical and anatomic details of the six cases follow

CASE 1—The patient, a man, aged 49, widower, cabinet maker by occupation, was admitted to the medical service of Dr Robert Carlisle The patient stated that for the past three years he had suffered at intervals from shortness of breath, palpitation of the heart and precordial pains The attacks had never been of sufficient severity to incapacitate him for work until about three months before admission, when, in addition to other troubles, he noticed that his feet and ankles were swollen Later the thighs and scrotum became similarly affected

Physical Examination—This showed a well nourished, well developed man, who was in great distress, orthopnea being marked The area of cardiac dulness was enlarged in all directions The apex beat of the heart was visible and palpable in the sixth interspace on the left side 13 cm to the left of the middle line There were no murmurs The heart was exceedingly irregular, gallop rhythm being present The pulse was rapid and irregular, the rate varying between 104 and 128 beats to the minute, once having reached 148 The lower extremities, scrotum and anterior abdominal wall were edematous, and the face was puffy The specific gravity of the urine was 1 022, it was acid and there was a trace of albumin with a few hyaline and granular casts The Wassermann reaction was negative The blood pressure was 158/100 mm Hg The non-protein nitrogen of the blood was slightly in excess of the normal, 55 mg having been found to 100 c c of blood Exophthalmos, tremor and enlargement of the thyroid were not detected Ophthalmoscopic examination was negative

Necropsy—Autopsy 5372 The body was that of a well developed, well nourished man, 49 years of age, weight 180 pounds There was no exophthalmos and the thyroid was neither palpable nor visibly enlarged The pretibial tissues were edematous and the abdomen was distended by fluid The left pleural cavity enclosed a large amount of clear fluid and the lungs were congested and edematous Scattered through both lungs were numbers of hemorrhagic infarctions, and the smaller branches of the pulmonary artery contained partly attached thrombi

Heart The precordial area was enormous The pericardium enclosed 400 c c of clear fluid The heart was greatly enlarged and weighed 780 gm The right ventricle was dilated to a marked extent and its walls were hypertrophied, measuring 1 cm in thickness The muscular columns within the ventricle were greatly thickened and flattened and numerous delicate whitish streaks were visible in the muscle substance The conus arteriosus was markedly dilated and its walls were thickened The right auricle with its appendix was dilated and the musculi pectinati were hypertrophied and flattened, the covering endocardium thickened and opaque The left ventricle was greatly dilated, the musculature hypertrophied, measuring 2 cm in thickness, the muscle substance was firm, reddish in color and there were numerous delicate whitish streaks in it, together with fibrotic patches measuring from 0 5 to 1 cm in diameter The endocardium of the ventricle was uniformly opaque and thickened The left auricle was markedly dilated, its walls were thin and the endocardium thickened and lusterless Near the apex of the left ventricle were several grayish-red thrombi, some of which were attached to the endocardial wall, others were attached to and intercallated among the muscular columns The valves were normal throughout and the aorta and pulmonary artery were well preserved The mitral ring was 13 cm in circumference, the tricuspid 12 cm, with the heart laid open

The liver was normal in size and reddish brown The spleen was slightly enlarged, dark red in color, the follicles prominent The kidneys were slightly enlarged and the capsules stripped easily, leaving behind a brownish-red surface which was perfectly smooth Both organs showed areas of anemic infarction

The mucosa of the gastro-intestinal tract was congested and velvety in appearance

Thyroid The thyroid was enlarged and weighed 65 gm It was well contoured, reddish in color and no colloid was visible On section the cut surface showed numerous delicate, grayish streaks

Fig 1 (Case 1) —Heart showing the great thickening of the muscle substance of the conus arteriosus and the rest of the right ventricle, including the muscle columns

Anatomic Diagnosis —Marked hypertrophy and dilatation of both hearts, fibrosis of endocardium and of heart muscle, thrombosis of left ventricle, chronic interstitial thyroiditis, pulmonary thrombosis and hemorrhagic infarc-

tion of lungs, chronic passive congestion of viscera, anemic infarction of kidneys, anasarca

Microscopic Examination—Tissue was removed from seven different parts of the thyroid gland The microscopic preparations showed essentially the same changes in all localities The connective tissue was thickened and irregularly distributed, grouping the vesicles into islands of various shapes and sizes In places the vesicles were exceedingly small, approximately the size of those in the fetal thyroid Each vesicle was lined by a single layer of low columnar epithelium and was rounded and empty of colloid In other islands the vesicles were slightly dilated, and perhaps half of them were filled by colloid which in

Fig 2 (Case 1)—Heart showing the immense hypertrophy of the walls of the left ventricle, including the papillary muscles, the diffuse thickening of the mural endocardium, the perfectly preserved valves, and attached thrombi near the apex

places stained reddish, in other places only faintly pinkish In still other instances the vesicles were even more dilated and filled by smooth, reddish-staining colloid Here and there were vesicles which had undergone cystic enlargement and were filled by bright red colloid All of the vesicles were lined by a single layer of low columnar epithelium and there was no detectable suggestion of papillary infolding in any of them Lymphoid follicles were not found The connective tissue was moderately well vascularized

Microscopic examination of the heart showed slight enlargement of the individual muscle fibers and the nuclei were frequently large and hyperchromatic

Scattered among the muscle fibers were streaks or patches of moderately cellular fibrillar connective tissue The vessels were well preserved

Microscopic examination of the rest of the organs revealed nothing of importance in the present connection

CASE 2—The patient, a man, aged 50, was admitted to Bellevue Hospital complaining of shortness of breath and swelling of the lower limbs While in the hospital the swelling extended upward and involved the penis and scrotum The apex beat of the heart was neither visible nor palpable, but was located by auscultation in the sixth interspace on the left side near the anterior axillary line The sounds were of poor quality There was an apical systolic murmur transmitted toward the axilla The pulse was rapid and irregular, the rate varying between 54 and 160 per minute There were numerous moist râles, audible over the entire chest The urine contained a trace of albumin

Necropsy—Autopsy 2903 The body was that of a well developed, well nourished man The facial hairs were fine in texture The chest and axillae were almost bereft of hair, and the pubic hairs were sharply defined in a transverse direction The neck was full and rounded and the thighs were arching The skin was smooth and delicate There was nothing to indicate enlargement of the thyroid gland There was marked edema of the entire body On opening the thorax the right pleural cavity was found to be full of fluid There were small, healed tuberculous foci at the apices of both lungs and the lungs were congested throughout

Heart The pericardium contained a slight excess of clear fluid The heart was enormously enlarged and weighed 700 gm The visceral pericardium was thickened at intervals and numerous small, whitish nodules were scattered along the course of the anterior coronary artery and its branches Both auriculo-ventricuar openings were large, admitting four fingers with ease Both auricles were markedly dilated, especially the left The cavity of the right ventricle was markedly dilated and its walls were tremendously thickened, the papillary muscles were hypertrophied and flattened and the endocardium showed patches of sclerosis The left ventricle was dilated, the papillary muscles enlarged and flattened, the endocardium thickened in patches varying from 2 to 10 mm The wall of the ventricle measured 1 5 cm in thickness The valves were normal throughout

Thymus There was a small amount of what appeared to be thymic tissue in the fat of the anterior mediastinum The spleen was small and the follicles were prominent The intestines showed no lymphoid hyperplasia The thyroid was enlarged and dark brown in color The kidneys were congested and the right was the seat of a healed infarction The liver was congested

Anatomic Diagnosis—Dilatation and hypertrophy of both sides of the heart, sclerosis of endocardium, hyperplasia of thyroid, recessive status lymphaticus, chronic passive congestion of viscera, healed infarction of right kidney, anasarca

Microscopic Examination—The connective tissue of the thyroid gland was moderately increased in quantity and richly vascularized In places it occurred as thickened trabeculae, dividing the alveoli into islands of variable size, in other places it could be seen infiltrating its way between individual vesicles, separating them one from the other Here and there the stroma supported islands of vesicles of the fetal type, each being lined by a single layer of cuboidal epithelium The vesicles were rounded and empty For the greater part however, the alveoli were moderately dilated and filled by pinkish colloid Papillary projections into the alveoli could not be found

The heart muscle showed no noteworthy microscopic changes other than slight increase in the size of the individual fibers, marked hyperchromatosis of the nuclei and the presence of small streaks of moderately cellular connective tissue lying among the muscle bundles

Case 3—The patient, a man, aged 29, was admitted to the medical service of Dr Nammack with the statement that, eight months previously, he was suddenly seized with shortness of breath, and that within the past four weeks his feet had become markedly swollen

Physical Examination —This showed a well developed man who was extremely dyspneic There was distinct bilateral exophthalmos The pulse was rapid, irregular, compressible, and there was visible pulsation in the region of the external jugular veins The pulse rate never fell below 80, nor did it exceed 104 to the minute The urine contained a trace of albumin and many hyaline casts The apex beat of the heart was not visible, but was palpable in the fifth interspace on the left side 1½ inches to the left of the midclavicular line, and was weak and diffuse in character The area of cardiac dulness was increased about an inch in all directions There was an apical systolic murmur transmitted to the axilla Tremor and enlargement of the thyroid were not noted

Necropsy—Autopsy 2942 The body was fairly well nourished and moderately muscular The feet and the subcutaneous tissues of the chest wall were edematous The abdomen was distended by fluid and both pleural cavities contained about 300 c c The lungs were congested The right apex showed a few small calcified tuberculous foci The thymus was persistent, in places yellowish, as if replaced by fat, in other places fleshy

Heart The pericardium enclosed about 250 c c of clear fluid The heart was slightly enlarged The right auricle was dilated, its walls were moderately hypertrophied and the endocardium was opaque The right ventricle was dilated and the trabeculae were hypertrophied and flattened The conus arteriosus was hypertrophied and dilated The left ventricle was not hypertrophied, but the endocardium was opaque, as was that of the corresponding auricle The papillary muscles and chorda tendinae were normal The valves throughout were well preserved The aorta was small in caliber and the intima was unchanged The spleen was small and the follicles visible The liver and kidneys were congested, as was the mucosa of the gastro-intestinal tract In the mucosa of the ileum were numbers of somewhat hyperplastic solitary follicles, the agminated patches were not prominent There were enlarged lymphoid follicles at the base of the tongue and in the mucous membrane of the pharynx The thyroid was rather small and reddish in color

Anatomic Diagnosis—Hypertrophy and dilatation of the right auricle and ventricle, sclerosis of the endocardium, recessive status lymphaticus, chronic passive congestion of viscera, healed tuberculosis of lungs, anasarca

Microscopic Examination—The connective tissue trabeculae in the thyroid were numerous, broad, dense and poorly cellular, but richly vascularized, and were so distributed as to divide the thyroid tissue into rounded, oval, oblong or angulated islands made up vesicles, most of which were very small, lined by low cuboidal epithelium without papillary infolding or reduplication, many of them empty There were moderate numbers of slightly dilated alveoli, some of which enclosed smooth, light pinkish-staining colloid or colloid with a dirty bluish tint

Microscopic examination of the heart muscle showed no changes worthy of mention at this time

Case 4—The patient a negro man aged 52 was admitted to the medical service of Dr Warren Coleman, complaining of shortness of breath on exertion that had been present for three months past One week before admission the patient noticed that his ankles were swollen He was subject to severe and frequent cough, with moderate mucoid expectoration

Physical Examination—This showed a well nourished man, with marked dyspnea and constant cough The apex beat of the heart was located 5½ inches to the left of the middle line in the sixth interspace On the right side dulness extended 1½ inches beyond the edge of the sternum There was a soft

systolic murmur at the apex that was transmitted to the axilla The first sound at the base was replaced by a blowing murmur which was transmitted downward A presystolic murmur and thrill were detected in the tricuspid region The precordium showed a marked heaving impulse and there was epigastric throbbing The pulse rate varied between 76 and 108 to the minute The lower edge of the liver was felt at the level of the umbilicus The urine contained albumin and a few hyaline casts

Necropsy—Autopsy 2388 The body was that of a negro man There was marked edema of the lower extremities extending up the thighs and involving the scrotum The heart was markedly enlarged and lay so that the right margin of the ventricle was against the diaphragm The right side of the heart was greatly dilated and the walls of the right ventricle were hypertrophied The left ventricle was dilated and its walls thickened The muscle tissue of the interventricular septum was slightly fibrotic Both auriculoventricular openings were large, but the valves were normal throughout The aorta and pulmonary artery were unchanged

Both lungs were congested The spleen was small and the interstitial tissues thickened The kidneys were well preserved, except for small patches of capsular adhesions which, on being stripped away, left behind a slightly granular surface There was a wedge-shaped, anemic infarction near the outer border of the right kidney The liver was nutmeg in appearance The thyroid gland was enlarged and, on section, colloid-containing vesicles were visible

Anatomic Diagnosis—Hypertrophy and dilatation of both sides of the heart, fibrosis of the interventricular septum, chronic passive congestion of viscera, anemic infarction of right kidney, hyperplasia of thyroid gland, edema of thighs and scrotum

Microscopic Examination—The heart muscle showed patches of hyaline connective tissue scattered here and there, each containing numerous thin walled blood vessels The endocardium showed considerable fibrosis and hyalinization, few cellular elements being distinguishable Unfortunately, microscopic examination of the thyroid was not possible, the original preparations together with the material removed at necropsy having been misplaced

CASE 5—The patient, a man, aged 34, was admitted to the medical service of Dr Nammack The patient admitted having had a chancre twelve years previously Three months before admission he became dyspneic and noticed palpitation of the heart

Physical Examination—This showed edema of both legs and cyanosis The apex beat of the heart was visible and palpable in the sixth interspace on the left side The right border of cardiac dulness reached 1½ inches to the side of the sternum There was a systolic murmur at the base and a late diastolic murmur following The pulse was small, the rate varying between 40 and 130 beats to the minute Over the apex of the right lung anteriorly there were dulness and crepitant râles Examination of the sputum, which was blood tinged, showed tubercle bacilli The urine contained albumin and hyaline and granular casts The systolic blood pressure was 100 The Wassermann reaction was strongly positive

Necropsy—Autopsy 3638 The body was that of a fairly muscular man The skin was pale and there was moderate edema of the feet and legs and slight swelling in the region of the neck corresponding to the thyroid The external configuration was unlike that commonly encountered in status lymphaticus The abdomen was distended by fluid, as were both pleural cavities The lungs were congested and in the lower lobe of the left lung was a large, hemorrhagic, thrombotic infarction The upper lobe of the left lung showed numerous patches of fibrosis The tissues of the anterior mediastinum were edematous and there was a large, symmetrical, bilobed thymus which reached as far downward as the auricles of the heart and upward to the lower level of the thyroid On section it was pinkish and fleshlike The precordial area was large

Heart The precardium contained an abundance of fluid The heart was greatly enlarged and weighed 550 gm The right auricle was dilated, but its walls were not thickened The right ventricle was hypertrophied, particularly the conus arteriosus, and the ventricle was dilated throughout The muscular trabeculae were thickened and flattened The endocardium was thickened and opaque and, on section, whitish threadlike streaks could be seen in the muscular walls for a distance half way through their thickness The left ventricle was hypertrophied and dilated, the walls measuring 16 to 20 mm The valves were normal The liver was nutmeg in appearance The spleen was small, the trabeculae numerous and prominent and the pulp reddish The follicles were not visible The kidneys were congested, but otherwise unchanged The lymphoid follicles of the intestines were normal

The thyroid gland was enlarged and weighed 102 gm The shape was well preserved On section the gland presented a spongy appearance, due to the presence of numerous small colloid-containing vesicles

Anatomic Diagnosis—Hypertrophy and dilatation of both sides of the heart, marked fibrosis of the endocardium of the right ventricle, chronic passive congestion of viscera, persistent thymus, hyperplasia of the thyroid gland, hemorrhagic infarction of the lung, healed tuberculosis, anasarca

Microscopic Examination—Running through the thyroid gland in all directions were bands of smooth, dense, noncellular connective tissue from which smaller prolongations penetrated between the alveoli, grouping them into small islands, or surrounding individual alveoli and separating them one from the other The alveoli varied in both size and shape Most of them were slightly dilated All of them were lined by a single layer of cuboidal epithelium and papillary projections into their lumina were not to be found They were filled with smooth, bright red colloid material The fibrous trabeculae were well vascularized

Microscopic examination of the heart showed numerous streaklike or patchy connective tissue foci lying between the muscle fibers, compressing or replacing them

Case 6—The patient, a well nourished negro, aged 26, was admitted to the medical service of Dr Frank Meara with the statement that about a month previously he became short of breath, shortly after which he noticed swelling of the feet and ankles There was distinct bilateral exophthalmos and slight swelling in the region of the thyroid The pulse was rapid, varying between 96 and 104 beats to the minute The apex beat of the heart was located in the sixth interspace, 13 cm from the middle line on the left side There was a double murmur at the base and a rough systolic murmur at the apex The urine contained albumin and many hyaline and granular casts

The patient furthermore stated that, as a youth, he suffered from frequent "fainting attacks" attended by convulsions and biting of the tongue These attacks ceased when he was about 14 years of age

Necropsy—Autopsy 4340 The body was that of a well nourished negro man There was marked bilateral exophthalmos and the neck, corresponding to the site of the thyroid gland, presented a slight prominence The lower limbs were noticeably arched, the axillary hairs were only fairly well developed, the pubic hairs were of the feminine distribution, being sharply defined in a transverse direction, only a few stray hairs stretching toward the umbilicus, the chest was practically hairless, and the glans penis was small On section the peritoneal cavity enclosed a slight excess of fluid Both pleural cavities were similarly bathed, the lungs were large and, on section, showed the characteristic appearances of brown induration The precordial area was large The heart was greatly increased in size and weighed 640 gm The right side was markedly dilated, and the right ventricle was dilated and hypertrophied The wall of the ventricle measured 0 5 cm in thickness and the muscular trabeculae in its lumen were thickened and flattened The left ventricle was hypertrophied

its wall measuring 15 mm, and the cavity was dilated The mitral valve was thickened and retracted and there were small numbers of minute vegetations scattered along the line of closure The aortic valves were thickened and retracted and one of them showed a small pouchlike dilatation The valves on the right side of the heart were unchanged

The liver, spleen and kidneys were congested, but otherwise unchanged The thymus region was occupied by edematous fat and thymic tissue was not to be seen

The thyroid was enlarged, firm, light reddish in color and only a slight amount of colloid was visible to the unaided eye On section, both lobes showed innumerable grayish streaks corresponding to connective tissue prolongations The lymphoid follicles of the intestines were atrophic

Anatomic Diagnosis—Dilatation and hypertrophy of both ventricles of the heart, dilatation of the right auricle, sclerosis of the mitral and aortic valves, acute vegetative endocarditis of the mitral valve, bilateral exophthalmos, chronic interstitial thyroiditis, chronic passive congestion of viscera, brown induration of lungs, recessive status lymphaticus, anasarca

Microscopic Examination —Tissue removed from different parts of the thyroid gland showed the presence of innumerable large and small, dense, smooth, poorly cellular fibrous trabeculae interspersed among the colloid vesicles in such fashion as to surround almost every individual vesicle In occasional instances small groups of vesicles of the fetal type were to be seen lying in the connective tissue framework, practically all of them being empty The great majority of the alveoli were slightly distended, lined by a single layer of very low, almost flattened epithelium, and filled by smooth, pinkish-staining colloid

Microscopic examination of the lungs showed marked congestion of the blood vessels Moderate numbers of alveoli contained a few red blood cells and desquamated epithelium and an occasional pigmented phagocyte Most of the vesicles, however, were unchanged

In this patient the picture of exophthalmic goiter is almost complete, bilateral exophthalmos, enlargement of the thyroid gland and tachycardia serving to establish the diagnosis with reasonable certainty in spite of the fact that histologic examination of the thyroid gland failed to show the changes customarily found in exophthalmic goiter The hypertrophy of the left ventricle is undoubtedly to be explained largely on the basis of sclerotic changes in the aortic and mitral cusps The hypertrophy of the right ventricle and the dilatation of the right auricle are less easily accounted for, the presence of chronic passive congestion of the lungs scarcely serving this purpose The naked eye and microscopic appearances of the lungs were such as are commonly found in association with valvular defects in the left heart and are to be interpreted as secondary to circulatory disturbances They are exceedingly common and are never regarded as causative factors in the production of changes in the right heart

The history of "fainting attacks," convulsions and biting of the tongue occurring in early youth and ceasing at about the fourteenth year is interesting in connection with the bodily configuration and signs of recessive status lymphaticus as revealed by atrophy of the various lymphoid tissues In these circumstances it is reasonable to assume that the seizures in question were of the nature of anaphylactic

attacks such as are not uncommonly seen in subjects of status lymphaticus, and that cessation of the attacks took place coincidently with completion of involution in the thymus gland and diminution in the lymphoid tissues in other parts A very considerable percentage of epileptics present the bodily configuration and other signs of status lymphaticus and complete disappearance of the convulsive seizures may be observed as age advances Microscopic examination of the lymphoid tissues in such subjects shows the presence of innumerable necrotic foci in the germinal follicles, thus releasing nucleoproteins which serve to sensitize the patient Before the anaphylactic incubation period is at an end another shower of necroses occurs, in this way completing the anaphylactic cycle, the reaction varying in intensity from simple urticarial rashes to convulsive disorders of the epileptiform type or even eventuating in sudden death

The six cases just synopsized permit of two interpretations—one, that they constitute a clinical and pathologic entity, the other, that the condition is an atypical form of exophthalmic goiter

Among the arguments in favor of the first mentioned interpretation is that the condition, as observed in Bellevue Hospital at least, occurs only in adult males of a fairly advanced age, whereas exophthalmic goiter is seen most commonly in females below 30 years, and that all of the patients were well nourished, while in exophthalmic goiter there is marked loss of weight due to disturbances in nitrogenous metabolism The type of histologic change in the thyroid gland lends color to the view that the condition is distinct from exophthalmic goiter, in which, however, the histologic alterations in the thyroid gland are by no means uniform There is an histologic picture marked by proliferation and dilatation of the vesicles of the thyroid gland, with papillary infolding of the epithelium, that is present in a considerable percentage of all cases of exophthalmic goiter and is apparently otherwise unknown in human pathology Edmunds and others, however, have shown that if a portion of the thyroid gland be removed from an animal, the remainder, after the lapse of a certain period, exhibits compensatory hyperplastic changes with intravesicular papillary prolongations comparable to those of exophthalmic goiter A similar condition is found in a certain percentage of stray dogs, and, occasionally, in goats and sheep Moreover, if such dogs be given iodids in large doses the alveoli again become rounded, the papillary projections disappearing The administration of iodids, also, is said to prevent the development of intravesicular papillae after operative extirpation of a part of the thyroid (Marine, Kocher, MacCallum) On the other hand, the thyroid gland in exophthalmic goiter sometimes shows a histology which is not attended by the changes indicated, but

is characterized by structural deviations not to be distinguished from those of ordinary goiter In the cases outlined the histologic changes in the alveoli of the thyroid gland were all of the simple, nonpapillary type, that is to say, they were of the sort which may or may not occur in the thyroid in exophthalmic goiter, while the overgrowth of connective tissue was noticeably in excess of that usually encountered in that disease Thus the microscopic findings do not aid materially in the clinical interpretation Had it been practicable to make serial sections of the entire thyroid gland in all of the cases, it is possible that intra-alveolar papillae might have been found, thus establishing an histologic composite which, when it does occur, is specific Finally, the interpretation of these cases as a clinical and pathologic entity is supported by the fact that the increase in the size of the heart is enormously in excess of and different in distribution from that usually encountered postmortem in exophthalmic goiter, in which enlargement is apt to be confined to the left ventricle

Granting the validity of these arguments, it is none the less difficult to disregard the possibility that the cases under discussion represent examples of atypical, ill developed exophthalmic goiter Against this view it might be urged, of course, that the changes in the thyroid are incidental and have nothing to do with those in the heart, an objection which appears to be overcome by the observation that the changes in the thyroid are strangely constant for accidental happenings It might also be urged that the changes in the thyroid are secondary to chronic passive congestion, but sclerosis of the thyroid in these circumstances, if and when it occurs, does not reach the degree shown by the glands under investigation, while sclerotic changes of the same type, extent and distribution are not known in other viscera which have long been the seat of passive congestion In a case recently examined postmortem at Bellevue Hospital the aortic and mitral valves were greatly thickened and retracted, and the tricuspid valves were reduced to thickened, rounded, cordlike bodies, a degree of sclerosis rarely seen in the valves of the right side of the heart, even in a necropsy service as extensive as that of Bellevue Hospital The heart was markedly dilated and hypertrophied In this case the liver was pulsating and there was a jugular pulse, the thyroid was slightly enlarged, weighing 35 gm, and was deeply congested, so that conditions were apparently propitious for atrophy and connective tissue replacement As a matter of fact, microscopic examination of the thyroid showed innumerable closely packed colloid vesicles without a suggestion of connective tissue overgrowth However, if one insists on the construction in question and eliminates the thyroid gland as the cause of the enlargement in the so-called idiopathic cardiopathy, one is still left with the extraordinary

combination of an apparently unprovoked dilatation and hypertrophy of the heart associated with symptoms of partially masked exophthalmic goiter, a picture which still is worthy of contemplation from the standpoint of recognition at the bedside In this connection, also, it is interesting to note that Blum has shown that experimental production of stasis in the thyroid gland results in increased elimination of nitrogen and of inorganic phosphates, and is attended by increased rapidity of the pulse

CONCLUSIONS

1 The symptomatology of the condition described by clinicians as thyrotoxic cardiopathy is identical with the symptomatology of the lesion familiarly known among pathologic anatomists as idiopathic dilatation and hypertrophy of the heart The clinical features are characterized by signs of great increase in the size of the heart, with or without murmurs of relative insufficiency and with or without signs of decompensation, as shown by dyspnea, subcutaneous edema, transudation in the serous cavities, cyanosis and the like, by tachycardia, and, on occasions, by bilateral exophthalmos with or without detectable indications of enlargement of the thyroid Thus the symptoms are largely those of the cardiopathy, and signs of thyroid disturbance, such as tachycardia, tremor, exophthalmos and enlargement of the thyroid, if present, are apt to be projected into the background rather than to assume a prominent place in the picture Of these symptoms, the tachycardia is constant, and with the patient in bed and at rest, varies between 90 and 160 beats to the minute

2 Anatomically, the so-called thyrotoxic cardiopathy is characterized by great enlargement of the heart, due to dilatation and hypertrophy of all the chambers or of different combinations of chambers without valvular or pericardial, arterial, renal, pulmonary or other of the causes customarily invoked to explain enlargement of the heart

3 The so-called thyrotoxic cardiopathy is associated with definite structural alterations in the thyroid in the form of moderate changes in the size of the gland, overgrowth of the fibrous trabeculea, rearrangement of the architecture of the parenchyma, dependent on redistribution of the stroma, regeneration of vesicles and dilatation of the older alveoli, and variations in the amount and staining reaction of the colloid—a chronic interstitial and hyperplastic thyroiditis

I am extremely indebted to Dr H M Ray for valuable assistance The photographs are by Mr William B Morrison

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THE EFFECT OF DIURETICS ON THE GENERAL BLOOD PRESSURE IN ANIMALS WITH CONSTRICTION OF THE RENAL ARTERIES *

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Since the days of Traube[1] a mechanical explanation for the high blood pressure of chronic renal disease has frequently been advocated, the original theory postulating increased peripheral resistance in the kidney itself as the cause Failure of ligature of both renal arteries to raise the blood pressure materially was sufficient disproof of the theory in any such simple form Various modifications of it have been suggested Katzenstein[2] obtained a slight rise after incomplete occlusion of the renal arteries, and Alwens[3] by compressing the kidneys in oncometers In spite of the failure to produce any rise in blood pressure at all comparable to the hypertension of human nephritis, the obvious association of hypertension with those types of renal disease in which the renal arterial system is most compromised, in the absence of any other satisfactory explanation, has prevented the entire abandonment of the mechanical theory Furthermore, clinicians have always been impressed with the compensatory nature of hypertension

The following experiments were undertaken in the hope of affording further light on the tenability of Traube's theory under conditions of increased functional demand on the kidney It was thought possible that, if the renal artery were narrowed, but not occluded, and then diuretic substances administered intravenously, the compensatory nature of hypertension might be revealed Narrowing of the renal artery without obliteration was made possible by the aluminum band of Halsted[4] The diuretic substances used were sodium chlorid, urea and caffein, injected intravenously, in addition, the effect of epinephrin was tested With an aluminum band placed about the renal artery, no increased flow through the kidney can occur as a result of mere local vasodilatation If any reflex mechanism exists whereby diuretic substances can produce an increased flow through the kidney under these conditions, a rise in general blood pressure must occur If, on the other hand, no rise in general blood pressure and no diuresis fol-

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1 Gesammelte Abhandlungen, Berlin, 1856, **2**, 290, **3**, 440

2 Virchows Arch f path Anat, 1905, **182**, 327

3 Deutsch Arch f klin Med, 1910, **98**, 137

4 Bull Johns Hopkins Hosp, 1905 **16**, 346

lows, then the evidence for this particular view of the compensatory nature of hypertension would be lacking

TECHNIC OF EXPERIMENTS

The experiments were performed as follows As large a dog as obtainable was used and was anesthetized with paraldehyd A cannula was then placed in the carotid artery and connected with a recording mercury manometer for the registration of the arterial pressure, and another cannula placed in the femoral vein for the injection of the solutions The kidneys were next delivered through lumbar incisions and the renal arteries exposed A cannula was inserted in the left ureter and connected with an electrical drop recorder In Experiments 1 to 11 no further operative procedures were done at this time, but in Experiments 12 to 15 the right renal artery was now ligated

A control period was then begun, arterial pressure and urine flow being recorded on a kymograph When the blood pressure had become steady, the various solutions were injected into the femoral vein, a sufficient time being allowed to elapse between injections for the blood pressure curve to return to its former level, varying from ten minutes to one hour in different experiments The speed of injection was as nearly uniform as possible The aluminum band was then placed around the left renal artery with sufficient constriction to reduce markedly the pulsation distal to it, but not to abolish pulsation completely In Experiments 1 to 11, ligature of the right renal artery was also performed This operation sometimes required the administration of a small amount of ether

After a second control period, the various solutions were again injected through the femoral cannula in the same volume and the same order as before The dog was killed at the conclusion of the experiment before recovering from the anesthetic

The solutions tested, and the volumes used, were as follows

5 per cent sodium chlorid solution, 10 to 20 c c
5 per cent urea in 0 9 per cent sodium chlorid solution, 10 to 20 c c
5 per cent caffein solution 7 5 to 10 c c
1 in 50,000 epinephrin chlorid solution, 10 c c

The amount injected varied with the size of the dog In the bulk of the experiments 15 c c of the sodium chlorid and of the urea solutions, and 10 c c of the caffein and the epinephrin solutions were used

The experimental difficulties in adjusting the band so as to diminish, but not completely obstruct, the blood flow were considerable A number of experiments had to be abandoned because of failure to accomplish this, or because of clotting in the cannula, or death of the dog before the conclusion of the tests In addition, one of us (E W B) was called to active military duty before sufficient experiments had been performed, and the other (K H) must assume the responsibility for the later experiments and for the opinions expressed in this paper

In order to bring the results together in a clear manner, the blood pressure and urine-drop records have been measured on the tracings, and the figures from the eight successful experiments are given in tabular form The blood pressure figures give the rise, represented by +, or fall, represented by —, in mean carotid pressure expressed

in mm Hg The urine is calculated as drops per hour, because of the extremely scanty secretion obtained in parts of the experiment The two lines, before and after, refer to the observations made before the constriction of the left renal artery with the band, the right renal artery having been ligated previously

TABLE 1—Data of Experiments

Experiment Number	Control Period Urine, Drops per Hr	Sodium Chlorid: Bl Pr Change in Mm Hg	Sodium Chlorid: Urine, Drops per Hr	Urea: Bl Pr Change in Mm Hg	Urea: Urine, Drops per Hr	Caffein: Bl Pr Change in Mm Hg	Caffein: Urine, Drops per Hr	Adrenalin: Bl Pr Change in Mm Hg	Adrenalin: Urine, Drops per Hr
2 Before	60					Sl variations	420	+60	180
After	12					Unchanged	10	+40	15
8 Before	20	+2	'0	+2	20	−6	20	+40	60
After	8	+2	8	+2	8	−5	8	+25	8
10 Before	60	+3	60	+2	60	−12	180	+23	120
After	6	+10	6	+2	6	−15	6	+25	6
11 Before	60	+10	120	+4	120	−20	360	+17	240
After	120	+7	240	+2	150	−15	120	+12	120
12 Before	40	+6	140	+4	180	−20	240	+12	180
After	30	+6	43	+3	45	−5	30	+14	30
13 Before	60	Sl variations	180	Sl variations	120	−27	420	+25	540
After	150	Sl variations	180	Sl variations	240	−32	600		
14 Before	90	+3	240	+3	240	−25	480	+20	300
After	150	Sl variations	360	+3	360	−30	150	+19	150
15 Before	15	+5	60	+5	60	−25	45	+20	60
After	28	Sl variations	60	Sl variations	90	−15	60	+15	28

As may be seen at a glance, the results of these experiments as shown in the table are negative They give no support to the view that hypertension in chronic renal disease is a compensatory mechanism, brought into play when the renal arterial stream-bed is narrowed, by chemical or reflex paths, to counteract the effect on excretion of the locally diminished blood flow Their value is only that of negative evidence in general They do not disprove the compensatory nature of hypertension, but show that its demonstration is not to be had by the experimental method employed A similar study of animals in whom a constricting band had been left for a considerable period around the renal artery, simulating a chronic lesion, would be of interest, but external events prevented our undertaking it, as had been hoped

It gives us great pleasure to thank Prof Theodore C Janeway for his directions throughout the course of the experiment

CONTRIBUTION TO THE PHYSIOLOGY OF THE STOMACH

XLVI GASTRIC SECRETION DURING FEVER

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Beaumont[1] was first to observe that

> In febrile diathesis or predisposition from whatever cause the villous coat becomes red and dry, at other times pale and moist and loses its smooth and healthy appearance, the secretions become greatly vitiated, greatly diminished, or entirely suppressed, and mucous coat scarcely perceptible, the follicles flat and flaccid, with secretions insufficient to protect the nervous papillae When there are corresponding symptoms of disease, as dryness of the mouth, thirst, accelerated pulse, etc, no gastric juice can be extracted, not even on the application of alimentary stimulus Drinks received are immediately absorbed or otherwise disposed of, none remaining in the stomach ten minutes after being swallowed Food taken in this condition of the stomach remains undigested for twenty-four to forty-eight hours or more, increasing the derangement of the whole alimentary canal and aggravating the general symptoms of disease

Clinical and experimental evidence confirms these early observations of Beaumont Thus Gluzinski,[2] 1888, noted that not only is there a diminution of the quantity of gastric juice, but that during the entire duration of an infectious fever the gastric juice showed an absence of acid, and that with the cessation of fever, or somewhat later, acid reappeared During chronic fevers there was no apparent diminution of acid, Gluzinski therefore concluded that the diminution of gastric juice was less influenced by elevation of temperature than by infection

Sassecki[3] noted that the quantity of acid was not always diminished during fever, and that if dyspepsia was present before the onset of fever, it in itself might be the cause of the diminished secretion

Uffelman,[4] in an analysis of the vomitus of eight children during fever, always found a diminished secretion of gastric juice

Grunfelder,[5] in a series of experiments on two dogs, observed the effect of infection on gastric juice by means of the Pawlow pouch

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* From the Hull Physiological Laboratory of the University of Chicago

1 Beaumont, W Experiments and Observations on the Gastric Juice and Physiology of Digestion, 1833
2 Gluzinski L A Deutsch Arch f klin Med, 1888, **42,** 145
3 Sassecki Cited from Gluzinski, Footnote 2
4 Uffelman Die Diet in den acute fieberhaften Erkrankungen, 1877
5 Grunfelder Ztschr f exper Path u Therap, 1914, **16,** 141

Gastric secretion was markedly reduced in quantity, free and total hydrochlorid were also reduced, pepsin remained constant

Nichols[6] says there is usually a diminution or total suppression of hydrochloric acid in various fevers, while pepsin is apparently little reduced

Stockton[7] says that "the examinations of stomach contents in fever patients yield contradictory results and consequently are not always easily interpreted The secretion may be but little impaired, more often there is a deficiency in hydrochloric acid, with less deficiency in the secretion of ferments

It is thus seen that most observers report a diminished gastric secretion and a lowered acidity in fevers

We have undertaken to renew the study of the changes in gastric secretion during fever in order to determine the mechanisms involved in the changes

Procedure—We prepared a number of dogs with Pawlow accessory stomachs A period of ten days to three weeks was allowed each dog for recovery before we commenced our work

The dogs were fed a standard quantity (from 150 to 200 gm) of cooked meat and as much water as desired The gastric juice was then collected at hourly intervals for five hours In addition, the juice was collected one hour before feeding The temperature of the animal was taken hourly during the period of secretion and the next morning following the experiment, so that we were sure that we were dealing with normal dogs

Analysis of Gastric Juice—One c c of the total quantity of gastric juice secreted was titrated on the same day for free and total hydrochloric acid *Pepsin* was determined by diluting 1 c c of gastric juice with 10 c c tenth-normal hydrochloric acid and the amount of digestion calculated by the Mett's method

Chlorids—Van Slyke's method was followed, but we used 1 c c of gastric juice because we found that during fever the quantity of juice secreted was so small as to necessitate the use of small amounts in our determinations

I CHANGES IN GASTRIC SECRETION PRODUCED BY FEVER

Procedure—The experiments were conducted as follows Gastric juice was collected for one hour to obtain the amount of the continuous secretion, at the end of this period the temperature was recorded

An intravenous injection of either sodium nucleate (10 c c of a 10 per cent solution) or of killed culture of *B prodigiosus* was then given, and after five or ten minutes the animal was given from 150 to 200 gm of meat At times the animal would refuse to eat On such occasions forced feeding was resorted to, the meat being placed on the back of the tongue With each meal 150 c c of water was given

In several instances it was noted that the dogs vomited the food about one and one-half hours after the injection of the nucleate or the *B prodigiosus* When this occurred, the food, which was always undigested, was fed to the animal again

6 Nichols Am Jour Med Sc, 1911, **142,** 93

7 Stockton, C G Diseases of the Stomach, New York, 1914, p 217

RESULTS

The results are briefly summarized in the accompanying Table 1, and Figure 1, A and B

Table 1 shows that in a series of experiments conducted on three dogs the changes produced in the gastric secretion were remarkably constant The volume was reduced Thus, with normal temperature the volume was 27, 30 and 85 5 c c in Dogs 2, 5 and 10, respectively In fever, with temperature of 105 F, the volume was reduced to 10 4 c c, 5 5 c c and 7 1 c c

Total acid and free acid were markedly reduced

Pepsin was increased in two dogs, and diminished in one The increase is apparently dependent on volume

Chlorids are practically constant We wish to emphasize this fact here in striking contrast to the change in the total and free acid The secretion is mucous and ropy in character

We may, therefore, conclude from the foregoing that during fever there are definite changes in the gastric secretion which are chiefly a diminution of volume, diminished free and total hydrochloric acid, a percentage increase in pepsin, and a nearly constant percentage of chlorids We wish to note that these changes are present only during the febrile period, and that the next morning, the animals' temperature being normal, the gastric secretion was again normal

It is worthy of special emphasis that the injection of sodium nucleate or *B prodigiosus* produces marked disturbances in addition to elevation of the temperature Thus diarrhea, mucous and bloody stools occurred in most of the dogs Severe chills and severe prostration were often present, yet the following day the temperature was normal, the animal apparently well and the flow of gastric secretion normal Only when our control experiments showed a return to normal did we repeat the experiment on the same animal

The fact that in five experiments on one dog a killed culture of *B prodigiosus* produced results identical with those following sodium nucleate indicates that there is nothing in the drugs or toxins used which might interfere or alter gastric secretion, but that it is the fever and its reaction which are the basis of the results

II MECHANISM INVOLVED IN THE CHANGES OF GASTRIC SECRETION DURING FEVER

(*a*) *Rôle of Heat or Temperature Elevation* —In a recent communication by Meyer and Carlson[8] the effect of external heat was proved to be a factor in the depression of hunger contractions Salle,[9] by elevat-

8 Meyer & Carlson Am Jour Physiol, 1917, **44**

9 Salle Verhandl d 28 Versamml d Gesellsch f Kinderh, 1911, **72**, Jahrb f Kinderh, **74**, 627

TABLE 1—SUMMARY OF EXPERIMENTS AND CONTROLS ON THREE DOGS, SHOWING THE EFFECT OF FEVER ON GASTRIC SECRETION

Hr	Dog 2, Fed a Standard Diet of 130 Gm Meat				Dog 5, Fed a Standard Diet of 200 Gm Meat				Dog 10, Fed a Standard Diet of 200 Gm Meat			
	Normal Av 7 Exper		Fever* Av 5 Exper		Normal Av 8 Exper		Fever* Av 9 Exper		Normal Av 7 Exper		Fever† Av 5 Exper	
	Temp F	Vol Cc	Temp F	Vol Cc	Temp F	Vol Cc	Temp F	Vol Cc	Temp F	Vol Cc	Temp F	Vol Cc
1	101.9	6.7	104.5	1.8	101.7	7.3	104.9	0.9	101.5	24.0	104.8	1.3
2	101.8	6.3	106.1	2.2	101.6	6.6	105.5	0.9	101.4	19.8	105.9	1.4
3	101.9	5.2	105.7	2.1	101.7	6.1	105.4	1.0	101.5	16.6	105.6	1.3
4	102.0	4.7	105.1	2.6	101.7	5.4	105.3	1.3	101.6	13.1	104.8	1.9
5	101.9	4.1	103.7	1.7	101.8	4.6	104.1	1.3	101.5	11.9	104.4	1.2
Total		27.0		10.4		30.0		5.5		85.5		7.1
Total acid	0.3854%		0.1039%		0.4272%		0.1422%		0.4968%		0.0350%	
Free acid	0.3151%		0.0209%		0.3610%		0.0699%		0.4345%		None	
Pepsin	1.85 Mm		2.64 Mm		1.90 Mm		3.10 Mm		2.3 Mm		1.8 Mm	
Chlorids	0.495% Cl		0.480% Cl		0.511% Cl		0.459% Cl		0.495% Cl		0.416% Cl	

* Injection of sodium nucleate
† Injection of B prodigiosus

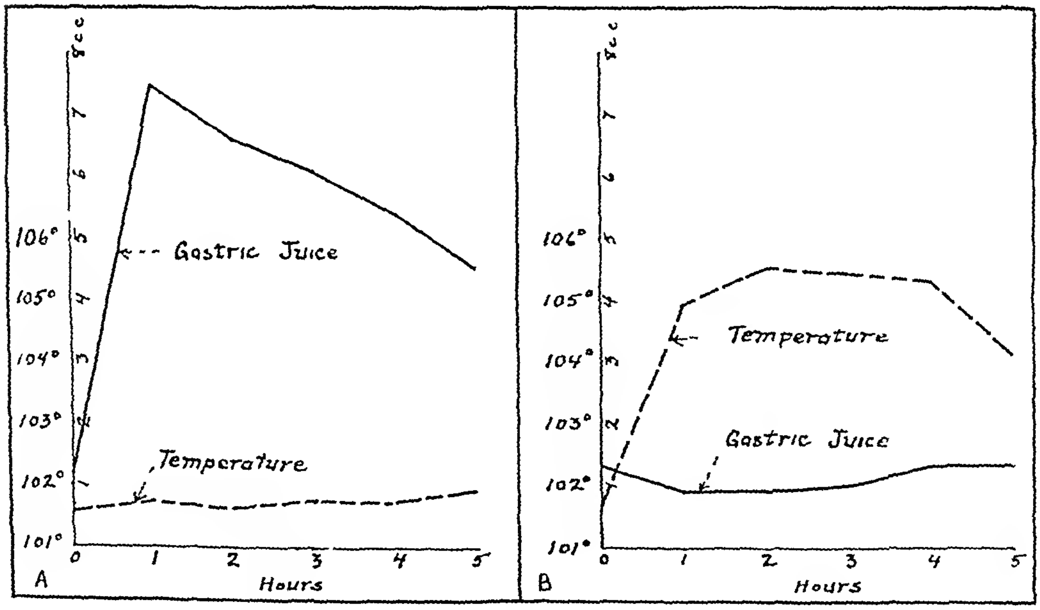

Fig 1—*A*, Composite chart of eight experiments (on Dog 5) showing the volume of gastric juice secreted after a meal of 200 gm of boiled meat Temperature normal

B, Composite chart of nine experiments (on Dog 5) showing changes in gastric secretion during fever produced by injection of sodium nucleate or *B prodigiosus* Food, 200 gm boiled meat

ing the external temperature, produced a condition simulating diarrhea in young dogs and reports a diminished volume, diminished free and total acid of the gastric juice Salle fed his animals milk only, and therefore his results are not conclusive

We determined the effect of elevating the temperature of the dogs by external heat, employing the method used by Meyer and Carlson[8] By using a stronger electric current we were able to obtain a temperature in the cage varying from 45 to 64 C

The normal temperature was first recorded, the animal placed in the hot box for one hour and the juice collected, at the end of this period the dog was fed The animal was kept in the box for two hours longer, the juice being collected separately each hour The animal was then removed to the room and the gastric juice collected for two hours at normal room temperature A series of three experiments on one dog were thus conducted

RESULTS

Table 2 and Figure 2, A and B, show the marked alteration in the character of the gastric secretion produced by elevating the temperature of the dog by means of external heat The results are almost identical with the results produced by fever itself A very striking fact is the entire absence of secretion on removal of the animal from the hot box, even though the body temperature fell rapidly to normal The gastric secretion was normal again within twenty-four hours

The animal becomes extremely prostrated for one to two hours after an exposure in the hot box Restlessness, dyspnea, rapid pulse and extreme exhaustion are present Salivation is pronounced, and this is a striking feature when compared with the decrease in gastric juice

We may therefore conclude that temperature elevation produced by external heat induces the same changes in gastric secretion as are produced by fever, experimental or infectious This is probably the condition of gastric secretion in cases of sunstroke

(*b*) *Effect of Fever Syndrome*—Does the fever or temperature elevation complex abolish the psychic factor, impair the function of the secretagogues or depress the gastric gland cells directly?

The striking similarity of the results obtained during actual fever and in the experiments of temperature elevation caused by external heat at once suggests the possibility of the entire change being due to failure of the psychic factor Thus Pawlow[10] says that "in the occasional illness of our experimental animals there is an augmented or a diminished activity of the peptic glands as contrasted to the normal," and he believes that the change in the secretion is "of a reflex nervous nature" We are able at present to differentiate between the psychic and the chemical factors by the use of gastrin[11] When gastrin is

10 Pawlow The Works of the Digestive Glands 1910, p 241

11 Keeton and Koch Am Jour Physiol 115, **37**, 481

TABLE 2—SUMMARY OF EXPERIMENTS (WITH CONTROLS) ON THE INFLUENCE OF THERMIC FEVER ON GASTRIC SECRETION

Hour	Dog 2—Fed a Standard Diet of 200 Gm Meat				
	Normal Average 8 Experiments		Fever Average 3 Experiments		
	Body Temperature, F	Volume Gastric Juice, C c	Body Temperature, F	Volume Gastric Juice, C c	Temperature of Box, C
1	101 6	7 3	106 6	1 3	48
2	101 7	6 6	108 5	0 4	47
3	101 6	6 1	105 9	0 1	45
4	101 7	5 4	103 9	None	21
5	101 8	4 6	103 0	None	21
Total		30 0		1 8	
Total acid	0 4272%		0 2066%		
Free acid	0 3610%		0 0942%		
Pepsin	1 90 Mm		2 6 Mm		
Chlorid	0 511% Cl		0 472% Cl		

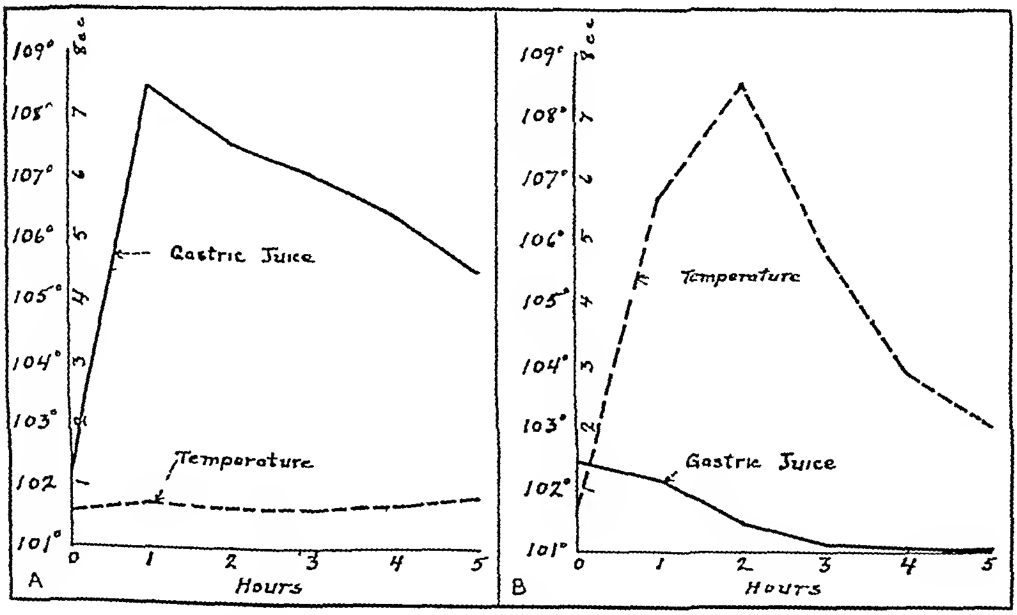

Fig 2—*A*, Composite chart of eight experiments (on Dog 5) showing the volume of gastric juice secreted after a meal of 200 gm of boiled meat Temperature normal

B, Composite chart of three experiments on Dog 5, showing change in volume of gastric juice during temperature elevation caused by external heat Food, 200 gm boiled meat

injected subcutaneously it gives rise to a definite secretion of gastric juice, in which the psychic factors play no rôle at all We therefore employed gastrin to determine the direct response of the gastric glands during fever

Procedure—We first determined the normal response of our animals to subcutaneous injection of 1 c c of gastrin Having secured our normals we determined the gastrin action during fever Our procedure was generally as in the preceding experiments The dog was allowed to secrete normally for one hour (continuous secretion), then sodium nucleate or *B prodigiosus* was injected intravenously At the end of the second hour 1 c c of gastrin was injected subcutaneously The juice was then collected at hourly intervals for from three to four hours after the injection of gastrin In some cases no analysis of the chlorids was made because of the small quantity of secretion

In studying the effects of temperature elevation due to external heat on the secretion caused by gastrin, we employed the methods detailed on page 358 with the addition that 1 c c of gastrin was injected

RESULTS

In a series of five experiments on two dogs in which fever was produced by nucleate and prodigiosus, and in twelve experiments on five dogs, in which a temperature elevation as high as from 105 to 112 was caused by external heat, the changes produced in the secretion caused by the injection of 1 c c of gastrin were striking and uniform The volume was diminished, at times there was no secretion at all The total and free acid were reduced The chlorids were practically constant (Tables 3 and 4, Figs 3 and 4, A and B)

These experiments prove that during fever produced by the injection of sodium nucleate or *B prodigiosus*, or during temperature elevation caused by external heat, gastrin is unable to induce the normal secretion of gastric juice The changes in the gastrin secretion are exactly the same as those found in the gastric juice secreted in response to food during fever

DISCUSSION

What other factor must be considered in the alteration of gastric secretion during fever?

Salle[9] believed that the heat of the body itself was the most important factor Grunfelder[5] considers the temperature of the blood together with the secretogogues as equally important Pawlow[10] holds that the changes are of a reflex nervous nature Our experiments demonstrate beyond doubt the fact that the heat of the body is an important factor in causing an alteration in gastric secretion

Furthermore, since, as we have proved that gastrin when injected subcutaneously during fever is unable to induce its normal secretion, it follows that any gastrin formed from the food substances eaten during fever would also be unable to induce a gastric secretion Our results with gastrin point to a definite depression of the gastric gland cells,

which may be explained by the action of "toxins" elaborated during fever It is conceivable that the toxins present might have a direct action on the glands We believe that the greatest factor in the alteration of gastric secretion during fever is a change in the cells of the glands of the stomach We are inclined to this view because of our

TABLE 3—SUMMARY OF EXPERIMENTS (WITH CONTROLS) ON TWO DOGS, SHOWING THE EFFECT OF INJECTION OF 1 C C GASTRIN ON THE SECRETION OF GASTRIC JUICE DURING FEVER

	Hour	Temperature, F	Volume, C c	Total Acid, per Cent	Free Acid, per Cent	Chlorids, per Cent	Pepsin, Mm	Remarks
Dog 5—Normal, secretion produced by 1 c c gastrin Average 3 experiments	1	101 4	15 6	0 4771	0 4314		1 0	Clear
	2	101 4	5 3	0 5044	0 4557	0 499	1 1	Clear
	3	101 5	1 6	0 3312	0 2188		1 4	Clear
	4	101 6	1 1					Clear
Total			23 6					
Dog 5—Fever, secretion produced by 1 c c gastrin Average 2 experiments	1	106 2	0 6	0 0912	None	0 431	4 3	Mucus
	2	105 6	1 0	0 1824	0 0639		3 3	Mucus
	3	104 8	1 2	0 1015	0 0406		4 6	Mucus
	4	103 4	0 5					Mucus
Total			3 3					
Dog 9—Normal, secretion produced by 1 c c gastrin Average 3 experiments	1	101 6	18 9	0 4497	0 3889	0 477	1 7	Clear
	2	101 3	13 8	0 4770	0 4132		1 2	Clear
	3	101 4	4 7	0 2764	0 1395		2 4	Clear
	4	101 6	1 9					Clear
Total			39 3					
Dog 9—Fever, secretion produced by 1 c c gastrin Average 3 experiments	1	105 6	1 4	0 0517	None	0 451	4 0	Mucus
	2	105 3	2 4	0 0669	None		3 5	Mucus
	3	104 6	1 5	0 0726	None		4 2	Mucus
	4	103 5	1 0					Mucus
Total			6 3					

results with gastrin Although the mechanism of the action of gastrin is not definitely understood, recent work would seem to indicate that it has a direct action in the cells of the gastric glands Thus in a personal communication from Luckhardt, Koch and Keeton on "Effect of Atropin on Gastric Stimulation of Stomach," they have noted that, "any dose of atropin sufficient to inhibit gastric flow under food stimulation will reduce the secretory activity following gastrin stimulation

It is always possible, however, even after maximal doses of atropin, doses that are definitely toxic to the animal, to cause a flow of juice by increasing the dose of gastrin" These findings tend to confirm our view We suggest that in fever gastrin is unable to induce its normal gastric secretion because of alteration in the gland cells We believe that the same mechanism explains the failure of gastric secretogogues

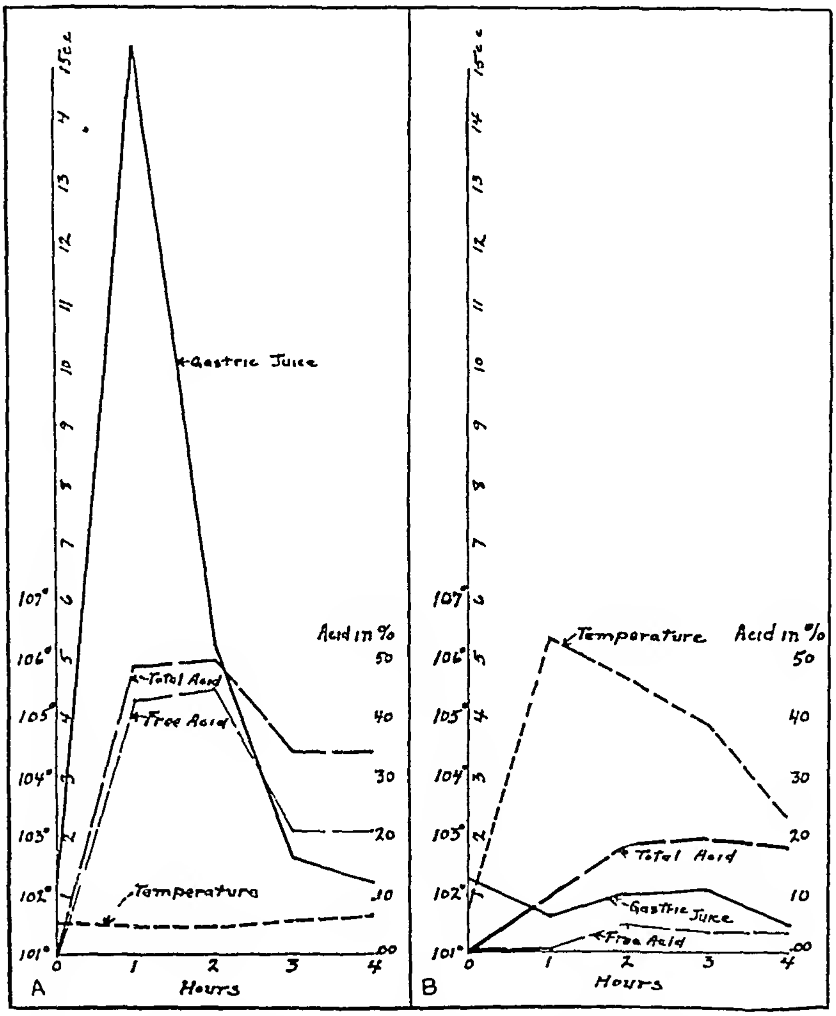

Fig 3—*A,* Composite chart of three experiments showing character of secretion produced by injection of 1 c c gastrin subcutaneously, during normal temperature

B, Composite chart of two experiments showing character of gastric secretion produced by gastrin during fever caused by sodium nucleate and *B prodigiosus*

produced by food eaten during fever to cause a secretion The most important factor in the alteration of gastric secretion during fever is a depression of the gland cells These cell changes are transitory in character, and are probably in the nature of a cloudy swelling

TABLE 4—SUMMARY OF EXPERIMENTS (WITH CONTROLS) ON FIVE DOGS, SHOWING THE EFFECT OF INJECTION OF 1 CC GASTRIN ON THE SECRETION OF GASTRIC JUICE DURING THERMIC FEVER

	Hour	Body Temp.,* F	Volume, Cc	Total Acid, per Cent	Free Acid, per Cent	Pepsin, Mm	Chlorids, per Cent	Box Temp., C	Remarks
Dog 11—Normal, secretion produced by 1 cc gastrin	1	101.6	14.1	0.4102	0.3190	1.6	0.480	25	Clear
Average 2 experiments	2	101.6	7.0	0.4193	0.3281	1.8			Clear
	3	101.5	3.7	0.2232	0.0912	2.7			Clear
Total			24.8						
Dog 11—Fever, secretion produced by 1 cc gastrin, dog in hot box	1	109.8	1.9	0.2275	0.1294	3.8	0.465	52	Mucus
Average 5 exper	2	101.5	0.7	0.1201	0.0401	2.5		24	Mucus
	3	100.6	0.7	0.0851	None	3.0		24	Mucus
Total			3.3						
Dog 12—Normal, secretion produced by 1 cc gastrin	1	101.2	11.0	0.5082	0.4417	1.3	0.504	23	Clear
Average 4 experiments	2	101.3	7.1	0.5287	0.4603	1.7			Clear
	3	101.3	3.5	0.3669	0.2621	2.0			Clear
	4	101.2	1.0						Clear
Total			22.6						
Dog 12—Fever, secretion produced by 1 cc gastrin, dog in hot box	1	109.2	2.9	0.3341	0.1456	2.6	0.489	49	Mucus
Average 3 experiments	2	105.2	0.6	0.1884	0.0144	2.8		42	Mucus
	3	102.8	0.5	0.0638	None			24	Mucus
	4	102.[illegible]	0.2					24	Mucus
Total			4.2						
Dog 9—Normal, secretion produced by 1 cc gastrin	1	101.6	18.9	0.4497	0.3889	1.7	0.477	21	Clear
Average 3 experiments	2	101.3	13.8	0.4770	0.4132	1.2		21	Clear
	3	101.4	4.7	0.2764	0.1395	2.4			Clear
	4	101.6	1.9						Mucus
Total			39.3						
Dog 9—Fever, secretion produced by 1 cc gastrin, dog in hot box	1	108.9	0.8	0.3322	0.2092	3.1		42	Mucus
Average 2 experiments	2	106.7	0.4	0.2462	0.1094			46	Mucus
	3	104.5	0.1					42	Mucus
	4	101.5	0.0					20	
Total			1.3						
Dog 14—Normal, secretion produced by 1 cc gastrin	1	100.0	26.3	0.4371	0.3873	1.2		23	Clear
Average 2 experiments	2	100.3	9.0	0.4288	0.3691	1.2		25	Clear
	3	100.2	1.0	0.1823	0.0866	2.4		23	Clear
	4	100.3	0.7						Mucus
Total			37.0						

* The fever was produced by elevating the external temperature by use of a hot box

TABLE 4—SUMMARY OF EXPERIMENTS (WITH CONTROLS) ON FIVE DOGS, SHOWING THE EFFECT OF INJECTION OF 1 CC GASTRIN ON THE SECRETION OF GASTRIC JUICE DURING THERMIC FEVER—(*Continued*)

	Hour	Body Temp.,* F	Volume, Cc	Total Acid, per Cent	Free Acid, per Cent	Pepsin, Mm	Chlorids, per Cent	Box Temp., C	Remarks
Dog 14 —Fever secretion produced by 1 c c gastrin, dog in hot box Average 1 experiment	1	109 0	0 7	0 3372	0 1824	3 1		35	Mucus
	2	105 1	0 6	0 1368	None	4 0		40	Mucus
	3	103 4	0 1					45	Mucus
	4	102 5	0 0					24	Mucus
Total			1 4						
Dog 16 —Normal, secretion produced by 1 c c gastrin Average 3 experiments	1	101 3	20 0	0 4740	0 4122	1 7			Clear
	2	101 4	20 7	0 5013	0 4466	1 8		23	Clear
	3	101 4	17 7	0 4922	0 4375	1 9		23	Clear
	4	101 4	11 2	0 4588	0 4132	1 7		23	Clear
Total			69 6						
Dog 16 —Fever, secretion produced by 1 c c gastrin dog in hot box Average 1 exper	1	109 9	1 2	0 1641	0 0821	2 5		48	Mucus
	2	103 2	0 3	0 1732	0 0274			26	Mucus
	3	102 2	0 0					25	
Total			1 5						

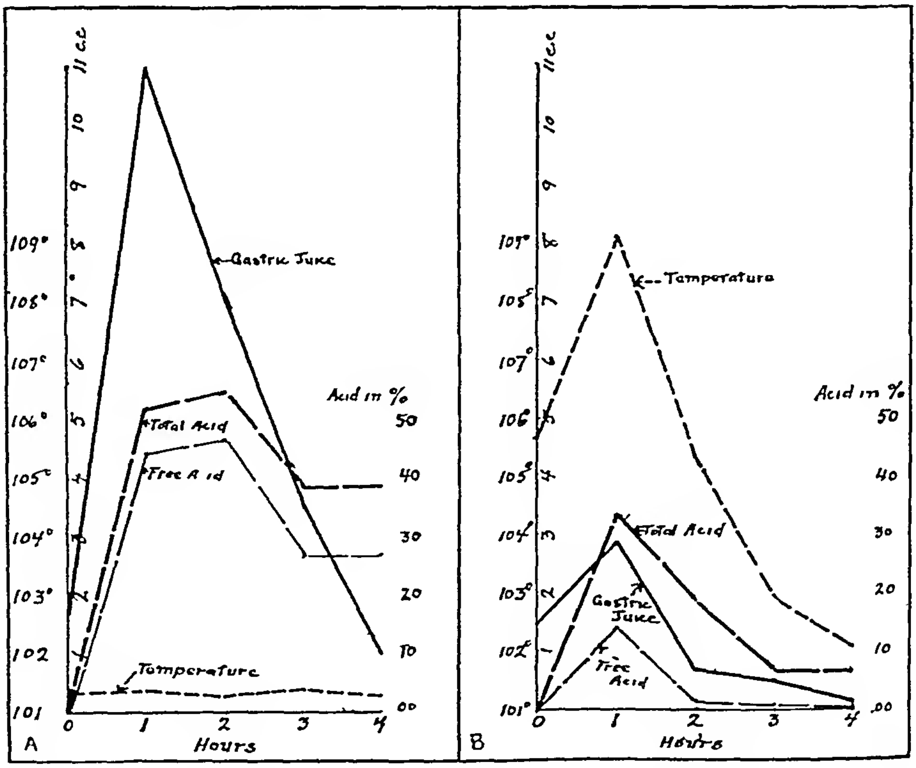

Fig 4—*A,* Composite chart of four experiments on Dog 12, showing character of secretion produced by subcutaneous injection of gastrin

B, Composite chart of three experiments on Dog 12, showing character of secretion produced by gastrin during temperature elevation caused by external heat

In view of the marked changes in gastric secretion in fever, these studies should be extended to other digestion secretions, especially those of the pancreas and the intestinal mucosa

SUMMARY

1 During fever gastric secretion is diminished in volume and in total and free acid The percentage of chlorids is constant or only slightly reduced and pepsin is relatively increased The secretion is ropy and mucous in character

2 External heat itself when sufficient to induce temperature elevation of from 2 to 4 F, will cause the same changes in gastric juice as produced by fever

3 Gastrin is unable to induce a secretion of gastric juice during fever, as well as in a condition of temperature elevation due to external heat

4 It is suggested that during fever, toxins are elaborated having a direct depressor action on the cells of the stomach so that they fail to react to the secretory nerve impulses and to the secretogogues

We wish to thank Dr F C Koch for his kindness in furnishing us with the gastrin preparations used in our experiments

INFLUENCES OF EXTRARENAL FACTORS ON THE RENAL FUNCTIONAL TEST MEAL*

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NEW YORK

FACTORS INFLUENCING TEST MEALS

Seeking to investigate renal function in both healthy and diseased kidneys in terms of their response to their most accustomed stimulation, Hedinger and Schlayer[1] studied their reaction to a twenty-four-hour standard diet Mosenthal,[2] continuing this method, revised their procedure and made it somewhat more adaptable to private practice and nonhospital patients His dietary contained about 13 4 gm of nitrogen, 8 5 gm of salt, and 1,760 c c of fluid, including a fair quantity of diuretic materials in the form of purins The twenty-four-hour diet was given in three meals at 8 a m, 12 m and 5 p m The urine was collected at two hour intervals from 8 a m, to 8 p m, and a night specimen from 8 p m to 8 a m of the following day, but no three day fixed diet was demanded preceding the last day, as was suggested by Hedinger and Schlayer Furthermore, Mosenthal felt there was no essential need for following out exactly the kind of meal he outlined, if only the subject partook of his three accustomed meals a day, took no food or drink between them, and followed the directions given for the collection of urine

This procedure proved to be, in his opinion, an excellent one for the test of renal function His normal subjects returned two-hour urinary specimens that varied 10 points in specific gravity between the highest and the lowest (later 9 points were accepted as the minimum normal variation) And the night urine was 1 018 or more in specific gravity with its nitrogen concentration above 1 per cent and a total volume of 400 c c or less The quantitative excretion of nitrogen, salt and water approximated the intake With a renal function impairment, the earliest change appeared in the night urine, the quantity increased, the specific gravity lowered and the nitrogen concentration was reduced Severe functional derangement manifested itself by a much lowered and constantly fixed specific gravity in all specimens and a diminished output of nitrogen, salt and water Later, Mosenthal

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* From the Harriman Research Laboratory and the Pathologic Laboratory of the Roosevelt Hospital

1 Hedinger and Schlayer Deutsch Arch f klin Med 1914 **114,** 120

2 Mosenthal The Archives Int Med, 1915, **16,** 733

and Lewis[3] in comparing several of the approved tests for renal function, namely, the phenolsulphonephthalein, nonprotein nitrogen and urea content of the blood, Ambard coefficient of urea excretion and the test meal, found the latter to be the most sensitive, in that it was relatively the first to disclose any degree of renal inefficiency

Aware of the possibilities of the influence of extrarenal factors on the test meal reaction, we undertook to study the degree of uniformity of response to the test meal by the same individual, the extent to which a lack of such uniformity might interfere with unqualified interpretations of the results, and to disclose, if possible, extra renal factors that may have operated to produce such variations in reactions All our subjects were persons going about their duties and leading their accustomed lives They were fed a standard diet, approximating that outlined by Mosenthal at a special diet kitchen, associated with the Laboratory of Roosevelt Hospital Each took the test meal for two, three or more days, usually consecutively, and carried out with care the instructions as to the collection of urine and abstinence from food and drink between meals

As concluded by Mosenthal, and too, as a result of our experiments (which already include over 200 test meals) variations in the specific gravity of the two-hour specimen of urine, and the volume and character of the night specimen, appear to be an index to the state of renal function, as elicited by the test The reaction of the kidney to the stimulus of the food given in the test meal truly represents the reaction for which the test was conceived and shows the actual renal factors involved in the reaction Influences from other sources serving to significantly affect the specific gravity variations, the volume or the nitrogen concentration of the night specimen must be looked at as complicating extrarenal factors The variations in specific gravity of the two-hour urinary specimens are functions of both the volume of fluid and amounts of solids excreted during each period, and it is quite apparent that extrarenal influences on one or the other of these factors can influence the periodic specific gravity variations

As for the excretion of water, the skin and lungs as well as the kidneys are excretory organs The loss of water from the body surface is subject to the physical laws which govern water evaporation and serves definite purposes Hence the influence on such fluid loss of atmospheric temperature, humidity and rate of air circulation This loss of water is a vehicle for the dissipation of body heat and is a factor in the mechanism for regulation of body temperature The remarkable constancy of body temperature in health stamps the mechanism of its regulation, and thus the operation of its several factors, as exceedingly

3 Mosenthal and Lewis Jour Am Med Assn, 1916, **67,** 933

persistent It is thus accorded priority over less persistent body functions and fluid supplied the kidneys for excretion must be secondary to the demand made at that time on the body fluids by the temperature-regulating mechanism

Investigating with the calorimeter the question of water excretion, Rubner[4] found that at a constant atmospheric temperature the water loss by skin was directly proportional to the relative humidity, an increase of water loss with an increase of atmospheric temperature, and further, that about 21 per cent of body heat produced was dissipated by water evaporation Gephart and Du Bois[5] estimated the amount to be in the neighborhood of 24 per cent Wolper and Peters,[6] studying the daily curve of water excretion through skin and lungs, found that it was not influenced by the time of day, as such, but was at a minimum during the late night hours or the day hours of sleep In other words, it was at a minimum when metabolism was at a minimum Further, the intake of food had no influence on the curve of excretion They found an average excretion of 70 gm of water per hour at 24 C, and 65 per cent relative humidity when the air was still Laschtschenko,[7] investigating the effect of water intake on water excretion from skin and lungs, found that it exerted no influence whatever To summarize then water loss by skin and lungs takes precedence over excretion by kidney, it is lowest when metabolism is lowest, it is not influenced by the intake of food or fluids and under ordinary circumstances must be nearer a liter (in the active man) than the 400 c c allowed by Mosenthal [2, 8] The fluid supply to the kidney consequent to such a preferential demand by the skin is gaged by the condition of water balance of the body, which, in turn, is manifestly influenced by the water intake

The reactions of Subjects S and B given in Tables 1 and 2, illustrating the tendency of the responses of most of our subjects to the test diet when taken for a few consecutive days, show a tendency toward concentration and reduction in the range of variations in

4 As quoted by A J Kalman, Pfluger's Arch f Physiol, 1906, **112,** 561

5 Gephart, F C, and Du Bois, E F The Archives Int Med, 1916, **17,** 902 The exact percentage of total heat given up to evaporation of water as found by an investigator is of course greatly influenced by the physical condition prevailing in the colorimeter, temperature, relative humidity and rate of air circulation

6 Wolpert and Peters Arch f Hyg, 1906, **60,** 299

7 Laschtschenko Arch f Hyg 1898, **33,** 145

8 Assuming 2,500 calories for the daily metabolism of a fairly active individual, and allowing a heat dissipation via water evaporation as equivalent to 25 per cent of the total metabolism, the actual water production in such a case would be as per calculation as follows 25 per cent of 2,500 cal = 625 cal, 0 6 cal for evaporation of 1 c c H_2O $\frac{625}{0\ 6} = 1{,}041$ c c H_2O

TABLE 1—SHOWING URINARY REACTION ON A TEST DIET

Student S, aged 22, laboratory assistant in good health

Date	Volume, C c	Specific Gravity	Nitrogen		Sodium Chlorid	
			Gm	Per Cent	Gm	Per Cent
12/6/16						
8 - 10 a m	140	1 022				
10 - 12 m	265	1 020				
12 2 p m	120	1 014				
2 - 4 p m	354	1 012				
4 6 p m	146	1 018				
6 - 8 p m	194	1 016				
Total day	1,519		7 10	0 47	11 4	0 75
Total night, 8 p m - 8 a m	340	1 026	3 69	1 00	3 35	0 99
Total 24 hours	1,859		10 79		14 75	
2/5/17						
8 - 10 a m	105	1 022				
10 12 m	200	1 020				
12 2 p m	156	1 022				
2 - 4 p m	154	1 023				
4 6 p m	187	1 021				
6 8 p m	242	1 016				
Total day	1 044				7 10	0 68
Total night, 8 p m - 8 a m	540	1 018			3 60	0 66
Total 24 hours	1 584				10 70	
2/6/17						
8 - 10 a m	80	1 020				
10 - 12 m	135	1 021				
12 - 2 p m	330	1 016				
2 - 4 p m	180	1 024				
4 - 6 p m	130	1 025				
6 8 p m	175	1 022				
Total day	1,030		8 6	0 83	6 7	0 65
Total night, 8 p m - 8 a m	380	1 024	2 7	0 72	2 5	0 65
Total 24 hours	1,410		11 3		9 2	
2/7/17						
8 10 a m	105	1 022				
10 12 m	175	1 022				
12 - 2 p m	185	1 024				
2 - 4 p m	165	1 024				
4 6 p m	120	1 026				
6 - 8 p m	335	1 015				
Total day	1,085		12 0	1 1	7 1	0 65
Total night, 8 p m - 8 a m	610	1 016	6 8	1 1	4 2	0 70
Total 24 hours	1,695		18 8		11 3	

TABLE 1—Showing Urinary Reaction on a Test Diet—(*Continued*)

Date	Volume, C c	Specific Gravity	Nitrogen		Sodium Chlorid	
			Gm	Per Cent	Gm	Per Cent
2/8/17						
8 - 10 a m	60	1 025				
10 - 12 m	108	1 026				
12 - 2 p m	156	1 023				
2 - 4 p m	126	1 025				
4 - 6 p m	100	1 027				
6 - 8 p m	131	1 025				
Total day	681		4 8	0 70	2 2	0 66
Total night, 8 p m - 8 a m	325	1 025	2 5	0 77	2 1	0 65
Total 24 hours	1,006		7 3		4 3	
2/9/17						
8 - 10 a m	72	1 027				
10 - 12 m	60	1 028				
12 - 2 p m	98	1 029				
2 - 4 p m	94	1 029				
4 - 6 p m	120	1 029				
6 - 8 p m	132	1 025				
Total day	576		5 1	0 89	4 1	0 70
Total night, 8 p m - 8 a m	400	1 027	5 1	1 27	2 6	0 60
Total 24 hours	976		10 2		6 7	

The subject complained very much of thirst the last two days of the test On the single day (December 6) there was a variation of specific gravity from 1 012 to 1 022, 10 points Beginning with February 5, the variations between maximum and minimum for five consecutive days are 7, 9, 11, 4 and 4 points

specific gravity of the two-hour specimens The total fluid output fell steadily from day to day (2, 7, 17, Table 1 excepted) and the sodium chlorid elimination fell likewise The nitrogen excretion was not definitely interfered with by the progressive tendency toward oliguria This change in response of the kidney appears in spite of the identical stimulus to the kidney of food and fluid intake In general terms, such reactions as these are explained as due to an effort on the part of the body to prevent depletion of its fluids in order to keep constant the concentration of its solids It is difficult to explain what factors operated in any particular day's reaction to compel conservation of body fluids This conservation might have been due to excessive preferential demand for water by the skin, resulting from a marked increase in metabolism or exposure to atmospheric temperature and relative humidity most favorable for water evaporation On the other hand, the volume of fluid ingested may have been too low for the subject or

the solid intake too high When these latter factors are operating the concentration and fixation of specific gravity would become progressively more marked as the test days went on, as illustrated by the cases just outlined, then again, the test meal might have been given at a time when the tissues were in a state of fluid depletion In all events, it appears that the water balance of the body is in a state of apparently

TABLE 2—URINARY REACTIONS ON A TEST DIET

Subject B, aged 25, physician on house staff in good health

Date	Volume, C c	Specific Gravity	Nitrogen		Sodium Chlorid	
			Gm	Per Cent	Gm	Per Cent
2/13/17						
8 10 a m	120	1 026				
10 12 m	160	1 025				
12 - 2 p m	216	1 024				
2 - 4 p m	128	1 020				
4 6 p m	104	1 029				
6 8 p m	85	1 031				
Total day	813		6 7	0 82	6 1	0 75
Total night 8 p m - 8 a m	303	1 029	3 8	1 2	2 1	0 68
Total 24 hours	1,116		10 5		8 2	
2/14/17						
8 10 a m	82	1 028				
10 12 m	102	1 026				
12 - 2 p m	109	1 029				
2 4 p m	120	1 028				
4 - 6 p m	99	1 030				
6 8 p m	70	1 028				
Total day	582		6 3	1 1	7 9	1 3
Total night, 8 p m - 8 a m	276	1 031	3 9	1 4	1 0	0 36
Total 24 hours	858		10 2		8 9	
2/15/17						
8 10 a m	74	1 029				
10 - 12 m	55	1 030				
12 - 2 p m	124	1 028				
2 4 p m	70	1 029				
4 - 6 p m	80	1 033				
6 - 8 p m	49	1 031				
Total day	452		6 1	1 4	3 4	0 74
Total night, 8 p m - 8 a m	342	1 031	5 2	1 5	2 5	0 74
Total 24 hours	794		11 3		5 9	

The specific gravity variations for the three consecutive days are 11, 4 and 5 points

fine adjustment in the healthy individual, and this balance the body strongly seeks to maintain. Nor is it difficult to appreciate how the effort to preserve such a balance will, in a great measure, influence the maximum specific gravity in the test meal reaction, as well as the maximum variation therefrom.

Table 3 discloses the interesting fact that with the successive reduction of the total twenty-four-hour volume of urine there was a tendency toward a percentile increase of the night volume, or, in other words, a tendency toward a constancy of night volume in spite of successive diminutions in daily total volumes. It is to be recalled in this connection that water loss from the skin is at a minimum during the sleeping hours and consequently there is relatively more water available to kidney for excretion during that time. An extrarenal factor

TABLE 3.—Showing Percentile Increase of Night Over Day Volume

Date	Subject S						Subject B		
	12/6	2/5	2/6	2/7	2/8	2/9	2/13	2/14	2/15
Total day vol. c.c.	1,519	1,044	1,030	1,085	681	576	813	582	452
Total night vol. c.c.	340	540	380	610	325	400	303	276	342
Total 24 hr. vol., c.c.	1,859	1,584	1,410	1,695	1,006	976	1,116	858	794
Percentile ratio of total night to 24-hour volume	18	34	27	36	32	41	27	32	43

of a different order which will be mentioned later, however, may be the contributory cause in the test day of Feb. 7, 1917, of Subject S., where the night volume equaled 56 per cent. of the total twenty-four-hour volume. It is pertinent to recall in this connection the findings of Quincke,[9] who, in studying the urinary output of subjects who were not ill of nephritis, found that the average hourly output of the early morning hours (from 5 to 8 a. m.) was far greater than that for the twenty-four hours or the total night hours. To what extent, we may ask, did the minimum loss of water by skin and lungs during the night render possible the availability of fluids for the kidney at a time so removed from the last hours of water intake?

Mosenthal recognized the tendency toward a fixation of specific gravity at a high concentration in healthy subjects with oliguria,[1] and allows for it in a measure by taking the highest specific gravity of the day as a basis for estimating the normal variations in the urine of subjects taking the test meal.

9. Quincke, H.: Arch. f. Exper. Pathol., 1877, 7, 115.

It is well known that exposure to cold and chilling of body surface induce an increased flow of urine The causes of this phenomenon are apparently not identical in every instance and probably vary in particular cases Several factors may have operated in the production of the diuresis In the first place, the chilling of the body surface may have caused a constriction of surface vessels, secondary to which splanchnic dilatation to some degree, including renal vessels, might occur Secondly, the peripheral vasoconstriction shuts off water loss by evaporation from the skin, thereby allowing an increase of fluids at the disposal of the kidney Thirdly, one must consider the possibility of the response of the kidney through a nervous mechanism with the stimulation of the skin by cold as the source of the afferent impulse

Jungman[10] demonstrated by cerebral stimulation in animals that this nervous mechanism was not merely the expression of a vasomotor reaction, as shown by the character of the urine during the diuretic period This latter fact had not been studied by Ashner and Bechterew, who, prior to Jungman, had investigated diuresis produced by cerebral stimulation Jungman, keeping his animals on a fixed diet and comparing the urine of control days and immediate foreperiods with the period immediately following cerebral stimulation, found that the urine of the diuretic period contained an increase of sodium chlorid, due both to an increase in volume and in concentration, this at times reaching tenfold that of the control period and even exceeding at times the chlorid concentration in the blood Furthermore, separate specimens of urine drawn off at different times during a single diuretic period showed the volume and sodium chlorid concentration to be mutually independent The absolute nitrogen output was found to be fairly constant All these findings were independent of water intake, which was determined by control experiments Jungman, on the basis of these results, suggested that the stimulation of the renal epithelium might be a factor, and that vasomotor reaction was not the only phenomenon to explain the result of this nerve stimulation

The reactions of Subject O, as given in Table 4, show how chilling of the body surface can affect the test meal reaction

On the first day, Feb 13, 1917, the heating apparatus was shut off in the laboratory, and Subject O feeling uncomfortably cold all day, passed a total day volume of 1,864 c c as against 847 c c, 1,103 c c and 672 c c on the three subsequent days With this as the probable extrarenal factor, the diuresis was practically continuous all day, the specific gravity varying at the most 5 points, though the concentration was correspondingly lower Again, on the night of the third test day, Feb 15, 1917, after walking an hour and a half in the cold, he passed

10 Jungman Munchen med Wchnschr, 1913, **2**, 1760

TABLE 4—SHOWING HOW REACTION IS AFFECTED BY CHILLING OF BODY SURFACE

Subject O, aged 25, laboratory assistant in good health

Date	Volume, C c	Specific Gravity	Nitrogen		Sodium Chlorid	
			Gm	Per Cent	Gm	Per Cent
2/13/17 8 10 a m	286	1 017				
10 12 m	238	1 015				
12 - 2 p m	322	1 020				
2 4 p m	310	1 020				
4 6 p m	430	1 017				
6 8 p m	278	1 016				
Total day	1,864		9 30	0 50	14 1	0 76
Total night, 8 p m - 8 a m	630	1 019	5 2	0 80	4 3	0 68
Total 24 hours	2,494		14 5		18 4	
2/14/17 8 10 a m	74	1 024				
10 12 m	118	1 027				
12 2 p m	135	1 025				
2 - 4 p m	184	1 025				
4 - 6 p m	138	1 027				
6 8 p m	198	1 023				
Total day	847		12 0	1 4	6 3	0 75
Total night, 8 p m - 8 a m	280	1 029	4 8	1 7	2 0	0 70
Total 24 hours	1,127		16 8		8 3	
2/15/17 8 10 a m	50	1 025				
10 12 m	194	1 020				
12 2 p m	133	1 020				
2 4 p m	340	1 021				
4 6 p m	138	1 019				
6 8 p m	248	1 015				
Total day	1,103		9 3	0 84	8 4	0 76
Total night, 8 p m - 8 a m	790	1 016	5 6	0 70	6 0	0 76
Total 24 hours	1,893		14 9		14 4	
2/16/17 8 10 a m	72	1 026				
10 12 m	98	1 024				
12 2 p m	125	1 025				
2 4 p m	163	1 020				
4 6 p m	86	1 027				
6 8 p m	128	1 029				
Total day	672		9 2	1 37	5 1	0 76
Total night 8 p m - 8 a m	290		5 6	1 92	1 9	0 64
Total 24 hours	962		14 8		7 0	

about 500 c c of his total night specimen of 790 c c at 10 30 p m For the four test meals, the absolute nitrogen elimination for the twenty-four hours was relatively constant, both in the total night and day specimens, and as a necessary corollary the nitrogen concentration varied inversely as the volume The sodium chlorid concentration throughout the period was very constant, the increased volume not reducing, but showing rather a tendency toward increasing it The sodium chlorid output varied considerably, therefore, with the fluctuations in the volume of urine These urinary findings coincide with those of Jungman in the diuretic specimens, resulting from the stimulation of the fourth ventricle The influence of cold must be considered, for it can interfere considerably with the correct interpretation of the test meal Even as an influence for part of the day it will increase or decrease the maximum variation of the specific gravity, depending on whether the specific gravity of the specimens outside the period of its operation were high or low At night, especially, if the room is cold and the subject happens to throw off some of the coverings during sleep, thus exposing the body surface, the urinary findings may be identical with those described by Mosenthal as the earliest signs of impairment of renal function Influence on the renal nervous mechanism by emotional states could affect the reactions in a similar way

Subject P, aged 44 Her symptoms had been headache, dyspnea and weakness Hemoglobin 78 per cent, blood pressure 165/110, eyegrounds, slight arteriosclerosis Phenolsulphonethalein output, Feb 14, 1917, 58 per cent in two hours Blood picture, Feb 14, 1917, nonprotein nitrogen 42, creatinin 0 96, uric acid 3 8 mg per 100 c c The urine showed a faint trace of albumin and a few hyaline casts, with negative findings on several examinations

Subject T, aged 45, had complained of occasional headache and dyspnea Blood pressure 165/110 Blood picture, March 5, 1917, nonprotein nitrogen 28, urea 32, creatinin 1 5, and uric acid 4 0 mg per 100 c c The urine showed a trace of albumin and many hyaline and granular casts

Of the group of subjects with definite renal involvement we submit the reactions of two who previous to the test were on restricted diets for several months and who at the time of the tests were subjectively free of any symptom consequent to renal insufficiency We are here afforded an opportunity to observe the effect of dietary treatment on renal function as evidenced by this test, and, what is more to our present purpose, the influence on the degree of reliability of the test meal findings with the omission of the fixed diets for the several days preceding the test as suggested by Hedinger and Schlayer

Though no specific effort was made to investigate the effect of a previous dietary, the response of Subjects P and T to the test meal add further data to the discussion of nitrogen excretion in nephritics having difficulty with nitrogen elimination They had been put on a diet low in nitrogen and high in fluids, drinking usually a gallon of

TABLE 5—REACTIONS OF SUBJECT P

Date	Volume, C c	Specific Gravity	Nitrogen Gm	Nitrogen Per Cent	Sodium Chlorid Gm	Sodium Chlorid Per Cent
2/13/17 8 10 a m	336	1 009				
10 - 12 m	290	1 012				
12 2 p m	285	1 011				
2 - 4 p m	120	1 020				
4 - 6 p m	134	1 017				
6 - 8 p m	58	1 023				
Total day	1,223		4 4	0 36	7 7	0 63
Total night, 8 p m - 8 a m	240	1 023	2 4	0 99	1 6	0 68
Total 24 hours	1,463		6 8		9 3	
2/15/17 8 10 a m	25	1 030				
10 - 12 m	65	1 020				
12 - 2 p m	46	1 023				
2 - 4 p m	74	1 020				
4 - 6 p m	171	1 018				
6 - 8 p m	58	1 025				
Total day	439		4 3	0 98	3 2	0 73
Total night, 8 p m - 8 a m	888		4 1	0 46	6 5	0 74
Total 24 hours	1,327		8 4		9 7	
2/16/17 8 10 a m	71	1 019				
10 - 12 m	130	1 017				
12 2 p m	93	1 022				
2 - 4 p m	90	1 018				
4 - 6 p m	110	1 019				
6 8 p m	71	1 027				
Total day	565		4 5	0 79	4 1	0 73
Total night, 8 p m 8 a m	350	1 021	3 1	0 90	2 6	0 75
Total 24 hours	915		7 6		6 7	
2/20/17 8 10 a m	166	1 017				
10 12 m	65	1 021				
12 - 2 p m	82	1 020				
2 4 p m	85	1 022				
4 6 p m	128	1 022				
6 8 p m	124	1 025				
Total day	650		4 5	0 75	4 2	0 70
Total night, 8 p m 8 a m	590		4 0	0 68	4 1	0 69
Total 24 hours	1,240		8 5		8 3	

water a day This was continued until the test meals were given The reactions for the first day appear comparatively normal in both, allowing for the results that follow oliguria in Subject T In the successive test days, however, the findings correspond to the reaction of interstitial nephritics—an increased night volume, reduced nitrogen concentration (except that of Feb 16, 1917, Table 5) They show on all days, however, nitrogen retention The absolute nitrogen outputs show a fair degree of constancy for each of the consecutive days, and

TABLE 6—Reaction of Subject T

Date	Volume, C c	Specific Gravity	Nitrogen		Sodium Chlorid	
			Gm	Per Cent	Gm	Per Cent
3/5/17 8 - 10 a m	40	1 024				
10 12 m	36	1 028				
12 - 2 p m	96	1 026				
2 4 p m	46	1 024				
4 6 p m	76	1 027				
6 - 8 p m	90	1 025				
Total day	384		5 5	1 4	4 0	1 05
Total night, 8 p m 8 a m	240		4 0	1 7	2 2	0 92
Total 24 hours	624		9 5		6 2	
3/6/17 8 - 10 a m	78	1 023				
10 - 12 m	168	1 019				
12 - 2 p m	164	1 021				
2 - 4 p m	304	1 015				
4 - 6 p m	114	1 014				
6 - 8 p m	292	1 013				
Total day	1,120		6 4	0 62	7 6	0 74
Total night, 8 p m 8 a m	495		3 8	0 72	4 0	0 81
Total 24 hours	1,615		10 2		11 6	
3/7/17 8 - 10 a m	72	1 023				
10 - 12 m	50	1 019				
12 2 p m	98	1 023				
2 - 4 p m	121	1 019				
4 - 6 p m	76	1 022				
6 - 8 p m	108	1 025				
Total day	525		4 9	0 93	5 2	1 0
Total night, 8 p m - 8 a m	670		3 9	0 58	6 7	1 0
Total 24 hours	1,195		8 8		11 9	

TABLE 7.—SUMMARY

Name and Date	Maximal Specific Gravity	Maximal Variation	Night Urine: Volume, C.c.	Specific Gravity	Nitrogen per Cent	Per Cent Above or Below 400 C.c.	Per Cent Above or Below 1% N Concentration
Normal							
Subject S							
12/6	1.022	10	340	1.026	1.0	—15	0
2/5	1.023	7	540	1.018		+35	
2/6	1.025	9	380	1.024	0.72	—5	—28
2/7	1.026	9	610	1.016	1.1	+53	+10
2/8	1.027	4	325	1.025	0.77	—19	—23
2/9[a]	1.029	4	400	1.027	1.27	0	+27
Subject O							
2/13	1.025	8	590	1.015	0.68	+48	—32
2/14	1.027	4	280	1.029	1.7	—30	+70
2/15	1.025	5	790	1.017	0.7	+98	—30
2/16	1.029	9	290	1.029	1.93	—27	+93
Subject D							
3/5	1.025	18	315	1.023	1.1	—21	+10
3/6	1.021	14	210	1.027	1.2	—48	+20
3/20	1.019	13	375	1.019	0.93	—6	—7
3/21	1.020	16	320	1.022	1.15	—20	+15
3/22	1.023	19	285	1.025	1.3	—38	+30
Chronic Interstitial Nephritis							
Subject G							
3/14	1.021	7	460	1.013	0.74	+12	—26
3/15	1.023	8	668	1.015	0.84	+67	—16
3/16	1.030	5	618	1.021	1.20	+55	+20
Subject P							
2/13	1.023	14	240	1.023	0.99	—40	—1
2/15	1.027	9	888	1.010	0.46	+112	—54
2/16	1.027	10	350	1.021	0.90	—13	—10
2/20	1.025	8	590	1.015	0.68	+48	—32
Subject T							
3/5	1.028	4	240	1.024	1.7	—40	+70
3/6	1.023	10	495	1.015	0.76	+24	—24
3/7	1.025	6	670	1.017	0.58	+68	—42
Subject L							
2/28	1.029	15	899	1.010	0.67	+125	—33
3/1	1.024	7	760	1.014	0.90	+90	—10
3/2	1.028	2	590	1.020	1.2	+48	+20

an equal degree for the day and night specimens when their eliminations are separately considered. The constancy appears to be one of total rather than of percentile elimination. Thus, Subject T., having difficulty with nitrogen elimination, can concentrate nitrogen as high as 1.7 per cent. in night specimens, and Subject P., as high as 0.99 per cent. Such variations in nitrogen concentration can appear, then, in the urine of individuals who have difficulty with nitrogen elimination, and it seems possible that a long continued diet low in nitrogen and high in fluids might have enabled them to respond quite normally, for one day anyway, to the renal test meal, though no concomitant power for increased total nitrogen elimination is evident.

A fair index of the reliability of any judgment based on a single test meal reaction in active individuals, healthy, or with slight, though definite, renal involvement, can be gathered from Table 7. Degrees of variations of specific gravity between maximum and minimum fluctuate markedly, and the variations do not necessarily diminish with the increase of maximum specific gravity, but may be quite the reverse (Subject D.). The night volumes, too, show decided fluctuations, varying, as in Subject O., from 98 per cent. above 400 c.c. to 27 per cent. below it on the following day. The nitrogen concentration of the night specimen shows a similar tendency to vary significantly above and below 1 per cent. (Subject T.); and the higher nitrogen concentration may occur with the specimen of lowest specific gravity (Subject S., Feb. 7, 1917). Finally, the range of variation of the composite test meal reactions is quite sufficient to enable one, by selective comparison, to demonstrate at times, on the basis of the accepted method of interpretation, the better reaction for the poorer kidney.

SUMMARY

The kidney is called on during the course of a day to respond to many influences other than the stimulus of ingested food.

Such extraneous influences are extrarenal factors affecting the test meal reaction.

Some of the factors we have been able definitely to identify, such as (1) the effect of the state of water reserve of the tissues and (2) the chilling of the body surface.

These factors can function significantly to distort the test meal reaction when viewed in the terms suggested by Mosenthal.

When so functioning they affect chiefly the fluid element in the test meal reaction complex, and this mainly by virtue of the fact that the skin and lungs make a preferential and significant demand on body fluids, whereas the excretion of solids by the skin and lungs is practically negligible.

These varying extrarenal influences are sufficient to require judgment with reservation as to renal functional efficiency on the basis of the suggested method of test meal interpretation, especially

1 On the basis of a single test meal (unless the reaction gives evidence of marked renal insufficiency)

2 In individuals who are well enough to be about and are exposed to the diverse influences of temperature, relative humidity and rate of metabolism

3 In cases in which no strict control of the dietary of the test meal is attempted

By reason of these circumstances, early diagnosis, by this method of renal insufficiency, is hazardous unless frequent tests consistently show renal involvement

Studied as groups, the several classes of kidney nephropathies have presented the various types of pictures described for them by Mosenthal This last statement we submit as a summary of our findings in over 200 routine test meals to nephritic patients in the medical ward of Roosevelt Hospital

A STUDY OF PAROXYSMAL TACHYCARDIA, WITH ESPECIAL REFERENCE TO TACHYCARDIA OF VENTRICULAR ORIGIN *

WARREN T VAUGHAN, M D
BOSTON

Since 1913 there have been under observation in the wards of the Peter Bent Brigham Hospital eighteen patients with rapid heart possessing the characteristic features of paroxysmal tachychardia, namely, sudden onset and offset, constant, regular, rapid rate and typical electrocardiographic tracings These cases present, for the most part, the usual, oft described histories and physical findings In the majority of cases the pacemaker lies in the auricle, as demonstrated graphically Of this type there were sixteen cases

The second type includes such cases as show a ventricular origin of the impulse, during the paroxysms This occurs surprisingly infrequently Occasion is therefore taken to summarize briefly the previous similar cases that have found their way into the literature and to add two from our own series

Reports of cases electrocardiographically showing ventricular tachycardia and similar electric complexes are infrequent We herewith present a brief summary of descriptions of this and allied conditions

Hart[1] reports a case of paroxysmal tachycardia, with paroxysms arising from impulses of ventricular origin, from which we quote at some length because of the similarity to one of our cases The patient had for one year been troubled with palpitation and dyspnea, with some cough and mucous expectoration, but with no edema of the legs The heart was not enlarged and was essentially negative, except for a soft blowing systolic murmur heard at the apex The slow, regular rhythm was frequently interrupted by premature beats, followed by pauses, and again by short periods of rhythmic tachycardia at a rate of approximately 200 per minute The paroxysms lasted from a few seconds to three minutes and gave much precordial distress The premature beats frequently gave a bigeminal or trigeminal character to the pulse After leaving the hospital the patient was seen several times, employed in the heaviest kind of labor, and feeling perfectly well Electrocardiograms during the slow period showed a reduplicated P-wave, increased P-R interval, and a ventricular complex which was prolonged so as to

* Submitted for publication Dec 6, 1917
* From the Medical Service of the Peter Bent Brigham Hospital
1 Hart, T Stuart Paroxysmal Tachycardia, Heart, 1912, 4, 128

occupy 0 45 second Diastole lasted 0 33 second During the paroxysms the curves were identical in character to those of preceding ventricular extrasystoles and indicated also what was taken to be a reversed auricular activity due to the passage of the stimulus from the ventricle to the auricle During the paroxysms alternation was in evidence The premature ventricular contractions were sometimes of left-sided apical type, sometimes of right-sided basal type Hart concluded that his case of paroxysmal tachycardia offered evidence of damage to considerable portions of the myocardium, because of (1) damaged auricular tissue (abnormal P complex, dropped beat), (2) damaged junctional tissue (lengthening of P-R interval), (3) damaged ventricular tissue (abnormal QRS complex, ventricular beats of two types, periods of tachycardia, composed of ventricular premature beats, alternation)

Lewis[2] reports a paroxysm of tachycardia shown electrocardiographically to be of ventricular origin, which was of approximately five minutes' duration Experimentally he has produced, by ligation of a coronary artery, and by the administration of poisons such as digitalis, aconitin and muscarin, a sequence of events corresponding quite accurately to those described in the case reported in this paper, namely, ventricular extrasystoles, followed by ventricular tachycardia of short duration If the experiment, such as ligation of the coronary artery, is continued the ventricular tachycardia increases in rate to 300 or even 450 beats per minute and then goes over imperceptibly into fibrillation of the ventricles

Lewis[3] also reports a case which over a period of years showed single and successive extrasystoles, indicated by the electrocardiograph to be of ventricular origin The greatest number of successive ventricular extrasystoles recorded in this patient was eleven These formed the characteristic regular, rapid rhythm with which we are dealing Bigeminy and trigeminy were of frequent occurrence The patient on frequent admissions usually showed moderate symptoms of impaired heart action such as shortness of breath on exertion, precordial uneasiness and palpitation

Cohn and Fraser[4] report a case of "paroxysmal tachycardia of doubtful, possibly ventricular, origin" in which the paroxysms were controlled by pressure, especially over the left vagus nerve The paroxysms of tachycardia appear to have been of longer duration than those described by Lewis and by Hart and there was absent the high

2 Lewis, Thomas Mechanism of the Heart Beat, London, 1911
3 Lewis, Thomas Single and Successive Extrasystoles, Lancet, London, 1909, **1,** 382
4 Cohn, Alfred E, and Fraser, Francis R Paroxysmal Tachycardia and the Effect of Stimulation of the Vagus Nerve by Pressure, Heart, 1913, **5,** 93

incidence of ventricular extrasystoles Premature ventricular beats were, however, recorded at the onset of some of the periods of tachycardia, but the curves following these single beats showed a different complex, thereby indicating that the pacemaker was not located at the same point in the ventricular muscle as was the site of origin of the preceding extrasystoles

Lea[5] reports a very interesting case of auricular fibrillation associated with a high degree of auriculoventricular block and with attacks of paroxysmal tachycardia This case had presented the findings of auricular fibrillation for probably two years previously Administration of digitalis produced first, partial heart-block, then complete heart-block, and then there ensued, at intervals, paroxysms of rapid, regular rhythm showing by the polygraphic tracings the ventricular type of venous curve From accurate measurements Lea assumes that the ectopic beats are of ventricular origin Premature beats between paroxysms were relatively frequent He suggests that this new rhythm formation may be the result of digitalis action and notes that within a few hours after the discontinuance of digitalis, the attacks disappeared entirely The highest number of consecutive beats recorded in a single paroxysm was 59, occurring during a period of 29 5 seconds, with a pulse rate of 120 No electrocardiograms were made

White[6] describes a case of gross cardiac arrhythmia which without graphic study might easily have been mistaken for auricular fibrillation The condition resulted from an unusual combination of ectopic ventricular contractions, arising from at least three different points in the ventricle, and with an occasional additional extrasystole of supraventricular origin Bigeminy was frequently present Only rarely were short runs of normal rhythm to be found Electrocardiograms showed the presence of defective conduction in the right branch of the atrioventricular bundle

A case is reported by Hoffmann[7] in which a paroxysm of auricular tachycardia was shown electrocardiographically to terminate with a series of atypical electrical complexes which persisted over a period of two seconds The onset of these atypical complexes was marked by two ventricular extrasystoles and the subsequent electrical variations corresponded quite remarkably to the curves obtained experimentally on the heart of a dog with ventricular fibrillation Following the last of these unusual complexes was a pause of approximately four-fifths

5 Lea, E C Auricular Fibrillation with a High Degree of A-V Block, and Paroxysmal Tachycardia, Quart Jour Med, 1911-1912, **5**, 388

6 White, Paul D An Unusual Type of Gross Cardiac Arrhythmia, Jour Am Med Assn, 1915, **65**, 1276

7 Hoffmann, August Fibrillation of the Ventricles at the End of an Attack of Paroxysmal Tachycardia in Man, Heart, 1911, **3**, 213

second and then the heart took up a normal slow rhythm with occasional ventricular extrasystoles The events during these two seconds may have been due to successive ventricular extrasystoles arising in various portions of the ventricular musculature, but Hoffmann concludes that they were the result of ventricular fibrillation, his conclusion being based on the similarity to experimental curves obtained in the dog and on the fact that palpation over the carotid artery during this period showed complete absence of the pulse beat

Out of a series of four cases studied by Butterfield and Hunt[8] one is described in which the electric curves showed the presence of an undoubted ventricular origin The case was of a man who for some time had been suffering from auricular fibrillation, and with failing compensation the heart rate had risen to the neighborhood of 120 One day it suddenly rose to 150 and became quite regular This paroxysm lasted throughout four days Later, ventricular extrasystoles were frequent, and in all three leads the complexes of these extrasystoles correspond accurately to those of the paroxysm

Two cases of the type not having the customary supraventricular origin of the tachycardia have occurred at the Peter Bent Brigham Hospital and are reported here

REPORT OF CASES

CASE 1 —*A case of paroxysmal tachycardia showing impulses of auricular origin and, later, of ventricular origin*

History—A H (P B B H Med No 5742), aged 21, was admitted to the wards Dec 9, 1916, complaining of "pain and palpitation of the heart" His previous occupations had usually kept him indoors and had never been heavy work He denied history of alcohol, drugs, tobacco or venereal disease He drank no tea and but two cups of coffee daily Past history was negative with the exception of sore throat about twice each year and an attack of "rheumatism" in 1913, with which he was in bed from March 5 until July From his account it seems probable that the so-called rheumatism was not rheumatic fever He suffered cardiac pain for the first time in 1914 There were no other cardiac symptoms until a year before admission, when he had his first attack of palpitation He was a heavy eater and had occasional attacks of "dry heaves" which at times started his heart into "palpitation"

Present Illness—The present illness is as follows Palpitation on exertion first occurred one year previous to admission He had then dyspnea and no pain In the first half year he had only three or four of these attacks of presumably auricular tachycardia, but later he developed them as often as three or four times in a week As he described a typical paroxysm, the heart would beat about 200 per minute, things would get misty, he would become dizzy, sometimes nauseated, and with sudden cessation of palpitation he would feel all right again About two weeks before admission to the hospital the patient developed two unusually severe attacks, one of which lasted three hours and the second over twenty-four hours He was in Chicago at the time and as he boarded the train to return to Boston another attack started which lasted until he reached Boston He describes the trip as "terrible" On arrival the attack was stopped by pressure

8 Butterfield, H G, and Hunt, G H Observations on Paroxysmal Tachycardia, Quart Jour Med, 1913, 7, 208

on the eye This was one week before admission He had additional attacks of shorter duration during the interval, but they had changed markedly in character from those previously described He describes a typical attack now as follows The heart is thumping slowly, then comes one strong beat followed by a long pause and three or four short, small beats in rapid succession Then one or two strong beats again, which cause violent, painful throbs in his head This is repeated several times, then quite a pause comes, followed by one very painful hard thump, and next the heart runs away into a rapid succession of weaker, small beats, frequently up to 200 per minute and quite regular All of this is accompanied by some nausea, somewhat of a cough and marked precordial pain, the patient feels faint and occasionally vomits With these large pulsations frequently what he looks at seems to pulsate

Physical Examination—The physical examination revealed a well developed and nourished individual lying propped up in bed, anxious and apprehensive, apparently very much discouraged Tonsils were markedly hypertrophied, but not inflamed There was moderate postnasal catarrh Lungs and abdomen were normal Liver dulness extended from the fifth rib to just below the costal margin, where a smooth, pulsating edge was felt Examination of the heart shows a diffuse, heaving impulse over the apex, of maximum intensity in the fifth interspace, 11 cm to the left of the midline The left border of cardiac dulness measured in the sixth space, 14 cm from the midsternal line Retromanubrial dulness measures 7 cm from side to side The right border of cardiac dulness measured 2 cm from the midline No thrills were felt On auscultation there was a slow, fundamental rhythm frequently disturbed by extrasystoles, with compensatory pauses, many of the beats being stronger than the others, and occasionally going into periods of tachycardia with a rate of about 150 to the minute and quite regular Pressure on the eyeballs or on the supra-orbital ridge of either eye, when very marked, and occasionally vagopressure, would cause the tachycardia to cease, with a resulting slow rhythm (This slow rhythm would not persist long and during the night of admission the patient was having attacks of palpitation for a time as often as once every five minutes) When the heart was beating slowly, at the apex the first sound was replaced by a systolic murmur which was transmitted both into the axilla and into the back The second sound was followed by a diastolic murmur In the tricuspid area there was a less loud systolic and a diastolic murmur This was blowing in quality In the aortic region the second sound was nearly replaced by a murmur Here also there was a to-and-fro blowing murmur In the pulmonic region there was a more distant to-and-fro murmur P_2 was moderately sharp In the fourth left intercostal space a to-and-fro murmur with the second murmur low pitched and blowing was heard The first sound was not heard With the heart beating rapidly, at the apex there was only a systolic murmur The first sound was sharp The second sound was absent In the fourth intercostal space both sounds, then, were heard and there was a systolic and a diastolic murmur The radial pulses were Corrigan in type The rate varied in attacks from 92 to 180, although the patient said that it had been up as high as 200 The vessels were not markedly sclerosed Over the femoral arteries there was a pistol shot sound and a Duroziez sign Pressure over the femorals caused a lancinating pain, with occasional huge beats complained of A murmur was heard in the subclavian artery as a loud rumble close to the ear A marked systolic pulsation, not well sustained, was seen in the carotids and even up as far as the temporal arteries

Diagnosis—Chronic cardiac valvular disease, aortic insufficiency and mitral insufficiency, hypertrophy of the heart and paroxysmal tachycardia

Treatment—Soon after admission the patient received 0 015 gm of morphin sulphate which had to be repeated at the end of an hour Powdered digitalis leaves was started in doses of 0 1 gm every three hours

Course—Throughout the first thirty-six hours in the hospital the patient had a miserable time, his heart rhythm changing at frequent intervals from a slow regular rhythm through transitions of extrasystoles, in which bigeminy and

trigeminy predominated, to the rapid regular rhythm of the tachycardia It was during these transitions with the extrasystoles that the greatest distress was experienced, the patient complaining of the terrible thumping in his head This was probably a result of the aortic insufficiency and the consequent large pulse pressure present During the tachycardia, which at times went as high as 180 beats per minute, the distress was mostly precordial From the time of admission pulsus alternans was noted

Thirty-six hours after admission, at 7 00 a m and after a restless night, the patient passed into a curious state of unconsciousness from which he could not be aroused, and during which respiration was periodic in type, with forceful attempts at expiration, during which he would throw his head back and would jerk it convulsively, but without true convulsions, this alternating with long periods of apnea The pupils were normal in size and reaction The heart rate was 124 to the minute, quite regular, with no pulse deficiency, the pulse being of good quality The attack lasted fifteen or twenty minutes, after which respiration again became regular and consciousness returned

Throughout the day the patient felt much improved and the paroxysms of tachycardia became much less frequent, but there was an increase in the frequency of extrasystoles in which there occurred at times short runs of ectopic beats at a rapid rate, similar clinically to the rhythm in the preceding tachycardia These new, regular, rapid rhythms, however, yielded neither to vagopressure nor to ocular pressure As will be shown later, they were a result of new impulse formation occurring in the ventricles Digitalis was discontinued on this day after the patient had received in all 1 4 gm of the powdered leaves

During the following night he developed a second period of syncope which lasted nearly two hours and was similar in character to the first Electrocardiograms at this time showed no further new rhythm From this time the patient's condition improved both subjectively and objectively, the extrasystoles becoming less and less frequent, and finally disappearing During the last two weeks in the hospital the heart rate and rhythm remained absolutely normal with the exception of a moderate sinus arrhythmia The patient remained in the hospital in all twenty-six days, during the last eleven of which he was up and about, exercising quite freely and without return of symptoms The pulse remained constantly below 90 per minute

Roentgenograms taken during a paroxysm of tachycardia showed the transverse diameter of the heart to be 16 5 cm as contrasted with a transverse diameter of 15 5 cm taken when the heart rate was normal At no time during the course of the disease were there any signs of venous stasis Ten months after his discharge from the hospital, the patient was reported to be in good condition and doing relatively hard manual labor in a theater He has had no recurrence of paroxysms

Electrocardiograms —The accompanying curves, taken by Dr W S Wells, are reported through the kindness of Prof Henry A Christian

Figure 1 shows the three leads taken during the first twenty-four hours in the hospital and in it can be seen the auricular form of paroxysmal tachycardia P-waves are inverted and occur in the T-waves T-waves appear inverted also The heart rate is 160 to the minute There is no evidence in these curves of left ventricular hypertrophy It will be remembered that the transverse diameter of the heart was 16 cm and that the patient was suffering from an aortic lesion The tracings in black below the electrocardiographic curves present a pulse tracing taken with the Erlanger apparatus and Frank capsule They show the typical collapsing pulse of aortic insufficiency, and in

addition show that alternation of the pulse was present on admission Pulsus alternans is usually present with such rapid rates and is not of prognostic importance

In Figure 2 a, pressure on the right eye over a period of eight seconds caused a change from a rate of 150 beats per minute through temporary sino-auricular block, then two normal beats, and finally one

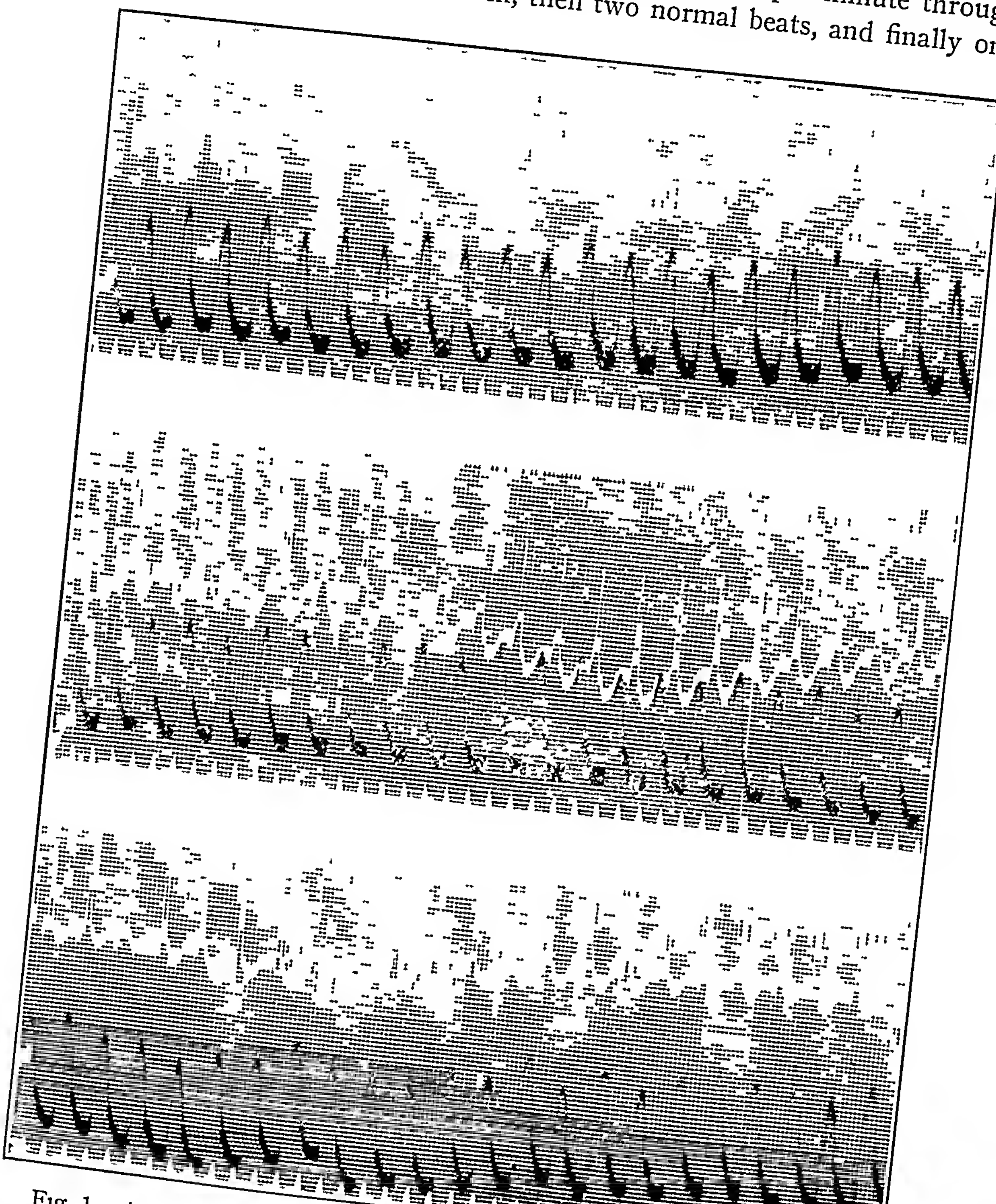

Fig 1—A H, Dec 9, 1916, 2 30 p m The ventricular rate is 162 Inverted P-waves occur in the T-waves The P-R time is about 6/25 second The tracing in black is a pulse record taken with an Erlanger apparatus and Frank capsule Diagnosis auricular tachycardia, pulsus alternans

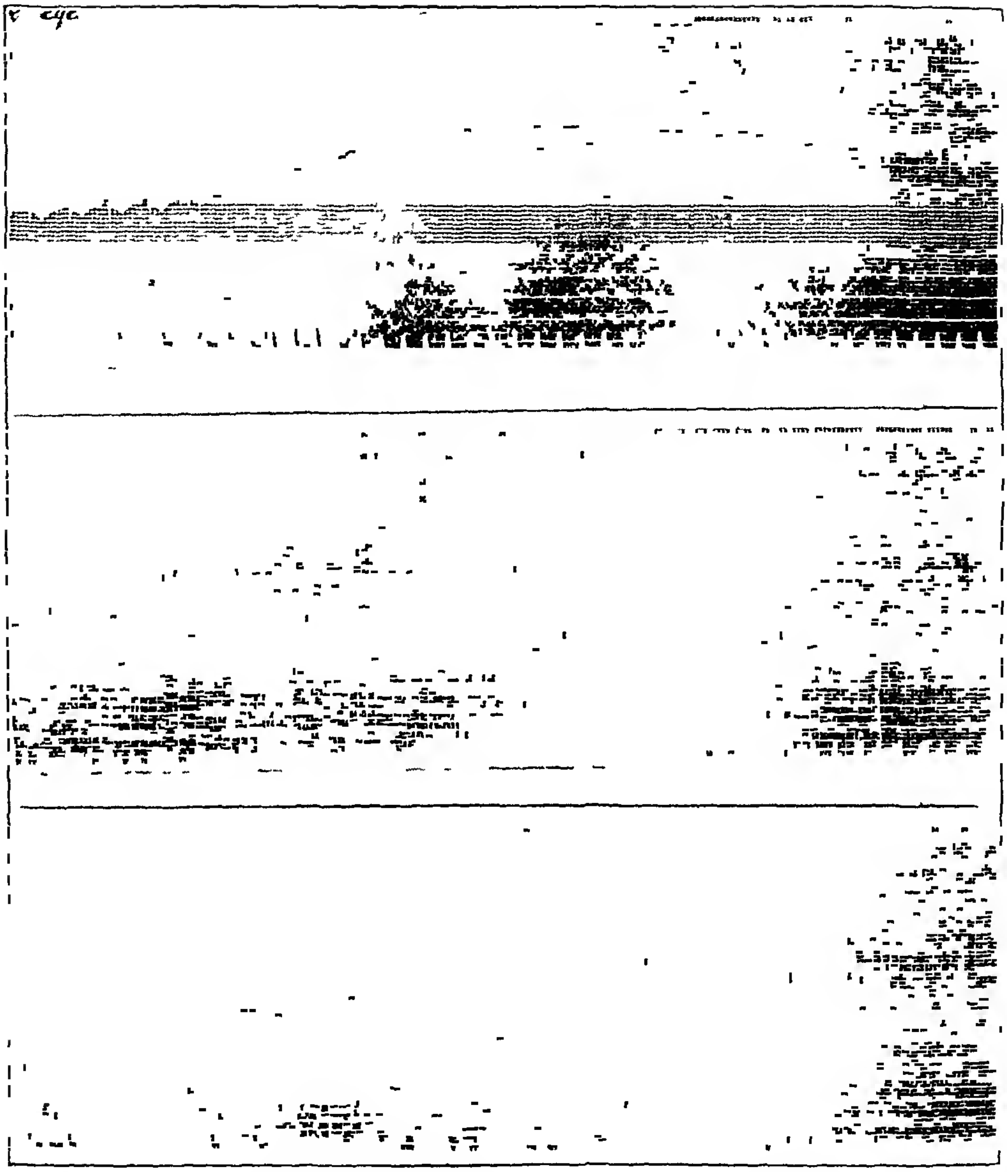

Fig 2—A H (*a*), Dec 9, 1916 The tracing shows that pressure on the right eye causes delayed conduction, S-A heart-block, A-V heart-block and then the heart picks up a normal rhythm with upright P-waves Pressure on the right and left vagus nerves was without effect At another time pressure on the left eye also caused a change from auricular tachycardia to normal, as shown by the electrocardiogram In both instances the heart was again in tachycardia within five minutes

(*b*) and (*c*), Leads 1 and 2, Dec 11, 1916, 10 10 p m A majority of the beats are extrasystoles arising in the left ventricle These occur in series of two to sixteen beats The P-waves cannot be made out in the ectopic complexes These tracings were taken during an attack of syncope and are, essentially, the same as those taken before and after the syncopal attack Lead 3 (not shown) shows the same type of curve as Lead 2, but with a deeper downward stroke

Diagnosis paroxysmal ventricular tachycardia

of auriculo ventricular block, to a normal rhythm with an upright P-wave and an inverted T The P-R interval is here four twenty-fifths of a second After the first ten normal beats the heart increased slightly, to 110 per minute Subsequently there occurred premature ventricular beats producing bigeminy and trigeminy, and within a few minutes the heart was again in auricular tachycardia (not shown on the curve) The curves of Figure 2 a were taken ten minutes after those in Figure 1 Twenty minutes later the same change from auricular tachycardia to normal rate was produced by pressure on the right vagus After normal rate persisted for a short time ventricular extrasystoles became frequent as before and in a few minutes more auricular tachycardia was reestablished Pressure on the left vagus caused no change in the auricular tachycardia

In Figure 2 b and c, taken two days later, are seen numerous ventricular extrasystoles, occurring sometimes in pairs or short runs, and interpolated with normal beats The normal P-waves preceding the beats of supraventricular origin are, as in the last curve, upright and tend to be doubled. Following the extrasystoles are pauses of about the length of diastole when the heart is at normal rate The longest period of ventricular tachycardia recorded on the tracings is of ten beats' duration Vagopressure and oculopressure while the heart was in this condition were without effect The P-R interval measures five twenty-fifths second The patient had received up to this time while in the hospital 1 4 gm of digitalis leaves How much he had taken before admission is uncertain, but it was probably a small amount The curves of Figure 2 b and c were taken during a syncopal attack described above, but were similar in every respect to those taken before and after the attack

Figure 3, taken eighteen hours after Figure 2 B and C, shows a predominance of the normal rhythm with a P-R interval of five twenty-fifths second and much less numerous, though still very frequent, ventricular extrasystoles producing in Lead 1 a bigeminy Pauses are fully compensatory P-waves as a rule show but one crest T-waves in all three leads are inverted The heart rate is about 95 per minute

Three weeks after the last tracings described and three weeks after digitalis had been omitted, the tracings of Figure 4 were taken, which show normal complexes with the exception of inverted T-waves in all three leads P-waves are all upright and the P-R interval measures five twenty-fifths second The heart rate is 73 per minute Heart sounds from the base of the heart are recorded by phonocardiogram and show a continuous vibration due to to-and-fro murmur Pulse tracings in Lead 3 fail to show definite evidences of alternation This is especially interesting when compared with the pulse tracings of Figure 1

This case shows in addition to evidence of severe cardiac damage by valvular disease, attacks of auricular tachycardia and later of ventricular tachycardia

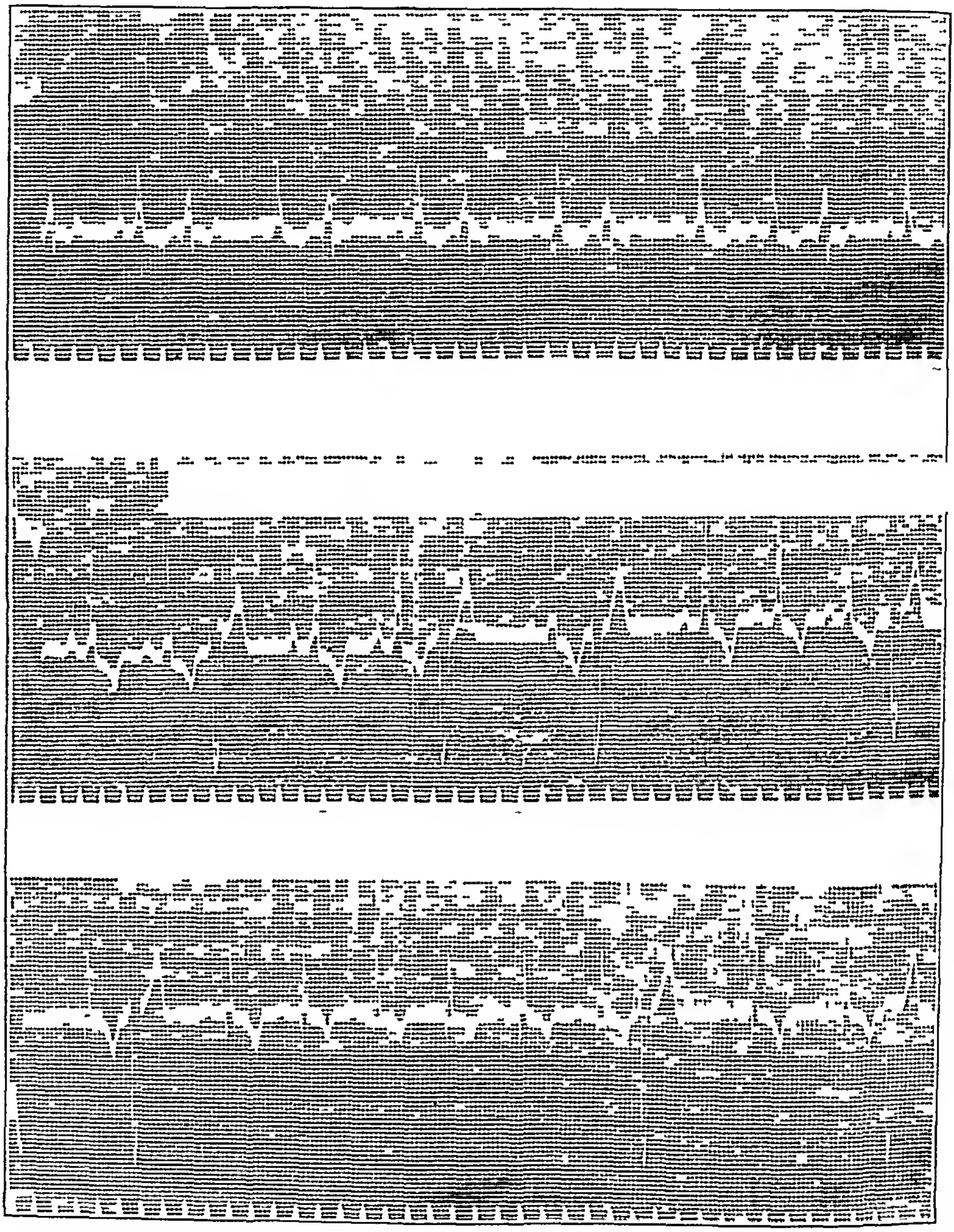

Fig 3—A H, Dec 12, 1916, 4 p m No runs of premature beats occur, as yesterday, but the extrasystoles are very numerous The T-waves are greatly depressed Diagnosis premature ventricular beats

There is evidence in this case, as in other cases quoted, of severe and widespread myocardial damage This is seen in the paroxysms of auricular tachycardia, the reduplication of the P-waves, the inverted

T-waves, the ventricular extrasystoles, the premature nodal beat, and, finally, the presence of definite valvular lesions In contrast to the curves obtained by Hart, all of the ectopic ventricular beats show the point of origin to be the same, apparently, in the left or apical portion of the ventricles, and there is no evidence of beats arising from the

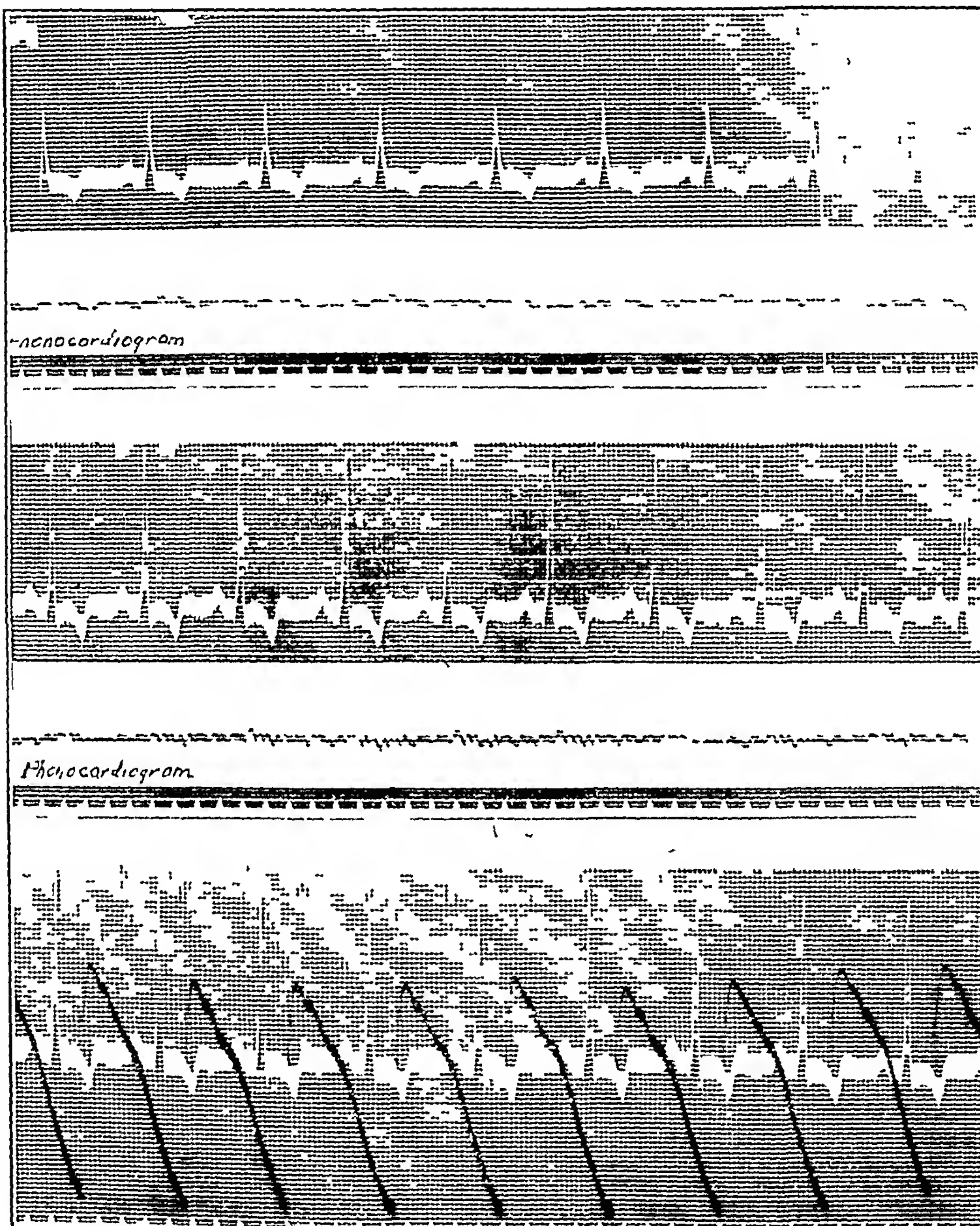

Fig 4—A H, Jan 3, 1917 In Leads 1 and 2 are records of the heart sounds at the base of the heart There is a continuous vibration due to a to-and-fro murmur Lead 3 shows a simultaneous pulse tracing The T-waves are inverted in all leads and the P-waves are upright The P-R interval is ⅕₂₅ second The R-waves are large in Leads 2 and 3 In previous curves occasional premature nodal and premature auricular beats have been recorded

right or basal portion All of the ventricular ectopic beats show a similarity, not only in the curves here produced, but also in other numerous curves taken

As regards etiology, digitalis may not be lightly ruled out It cannot be definitely proved with the evidence at hand that the cessation of symptoms within twenty-four hours after the discontinuance of digitalis in two somewhat similar cases (this case and that reported by Lea) is but a coincidence But the amount of digitalis used in our case was near the lower limits necessary for physiologic effect If digitalis is a factor, there must be an additional, and probably more important "predisposing" factor as contrasted to the former, which might be termed "exciting" This predisposing factor is in all probability a hyperexcitability of the damaged musculature In the case here reported the former effect is very slight, as evidenced by a normal P-R interval, whereas the latter is the dominant feature The incidence of aortic valvular disease in this case may be conceived to have some etiologic connection with the paroxysms of ventricular tachycardia when we consider that in such hearts the coronary arteries are frequently damaged and that Lewis[2] is able to produce experimentally ventricular extrasystoles and tachycardia by ligation of the coronary artery The possibility of this being a factor is further emphasized by the fact that the ventricular ectopic beats arise from but one portion of the ventricle

The attacks of syncope remain unexplained, but probably were greatly influenced by the condition of the peripheral circulation, the rapid and irregular beats being inefficient in pumping sufficient nourishment to the cerebral centers

CASE 2—*A case of paroxysmal tachycardia in which the site of impulse formation may be in the ventricle*

History—F N (P B B H Med No 5503), aged 50, was admitted to the wards Oct 25, 1916, and discharged improved, Nov 16, 1916 The patient's past history was essentially negative, except that he had used much alcohol during his life Twenty years previously he had had "malaria" for six weeks Also he had had a mild attack of gonorrhea when he was 19 years old One year before admission he had had an attack of indigestion with belching of gas two or three hours after meals and occasional vomiting of greenish material, which condition persisted for ten days Six weeks before admission he had a similar attack, which was accompanied by severe palpitation and a noticeably rapid heart Paroxysms of palpitation came at frequent intervals since and with increasing severity, usually lasting about fifteen minutes at a time and occurring every day during the previous three weeks Dyspnea and orthopnea had been very great, but there was no history of precordial or abdominal pain and no edema was present

Physical Examination and Course—On examination the heart was found to be slightly enlarged to the left and with a rapid, regular rate (from 150 to 180 per minute) which did not respond to vagus stimulation There was no pulse deficit The liver was enlarged and tender The lungs were emphysematous throughout Systolic blood pressure was 98 mm, diastolic 80 mm

The exact duration of the attack from which the patient was suffering at admission was uncertain, but it persisted throughout three days in the hospital Cessation was sudden and followed by a heart rate of 100 per minute With the heart beating slowly, a soft, blowing systolic murmur became audible in the apex region During the tachycardia various remedies were prescribed, including vagopressure, and morphin which was given to relieve the patient's distress One c c of digipuratum was given intramuscularly and this was followed by a course of digitalis During the paroxysm the patient's subjective condition became so grave that he was placed on the danger list Four days after the paroxysm had ceased the patient became extremely uncomfortable and com-

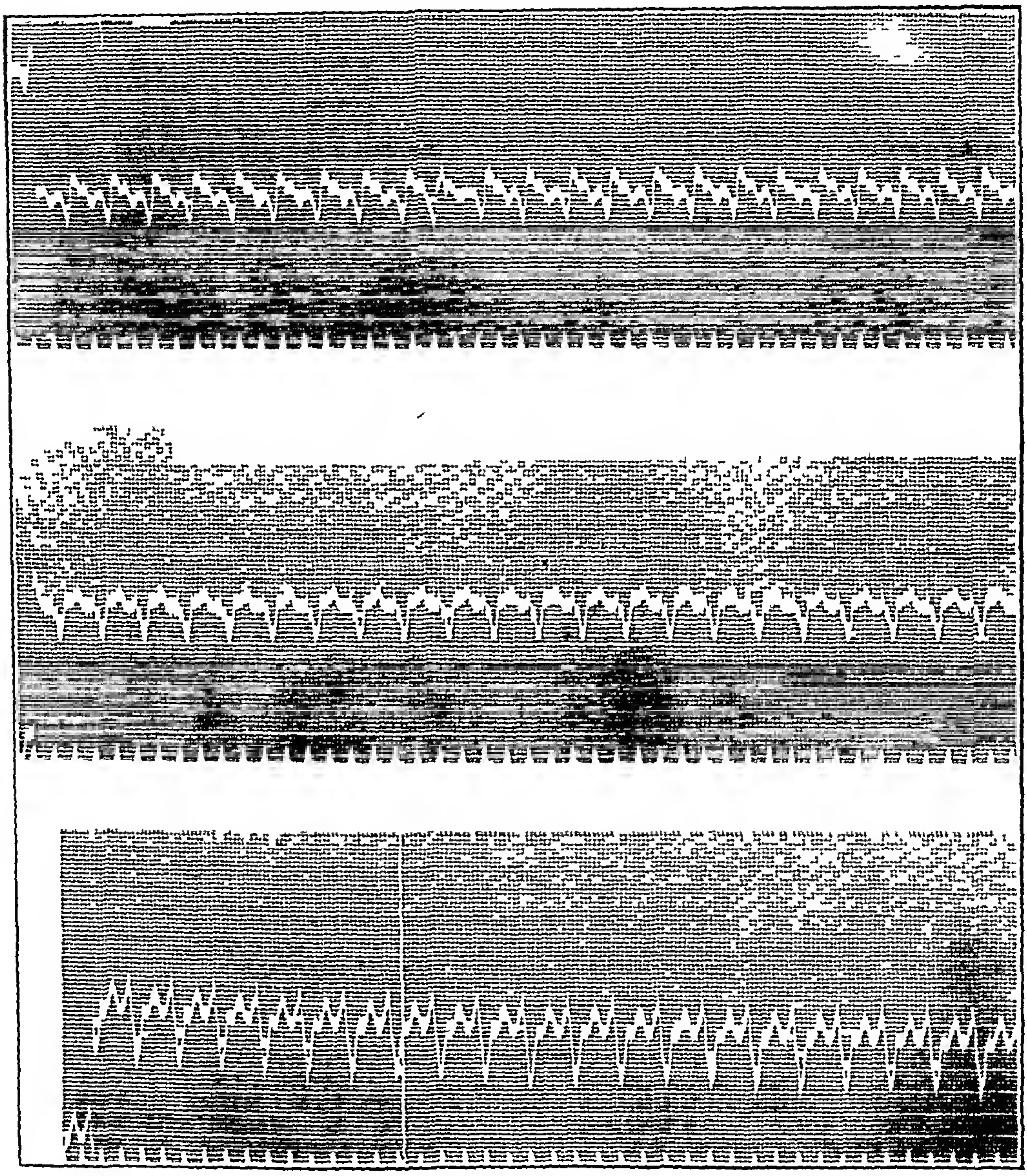

Fig 5—F N, Oct 26, 1916, 9 30 a m This is an unusual type of tachycardia No P-waves can be made out In Leads 2 and 3, the ventricular complexes look like those which might arise in the left ventricle, but in Lead 1 they are atypical Rate 150 In this curve occasional complexes come prematurely and are followed by a notch In other curves such premature complexes are not seen Pressure on the vagi and eye had no effect except slowing the heart Elevating the foot of the bed thirty inches had no effect Diagnosis paroxysmal ventricular tachycardia

plained of palpitation The heart at that time was beating around 160 per minute with every third or fourth beat a ventricular extrasystole, the premature beats not being felt at the wrist Bigeminy was also present at times This paroxysm of tachycardia with irregular rhythm lasted for three or four days, with occasional intervals of normal rhythm After this he had no recurrence and rapidly improved until the time of discharge

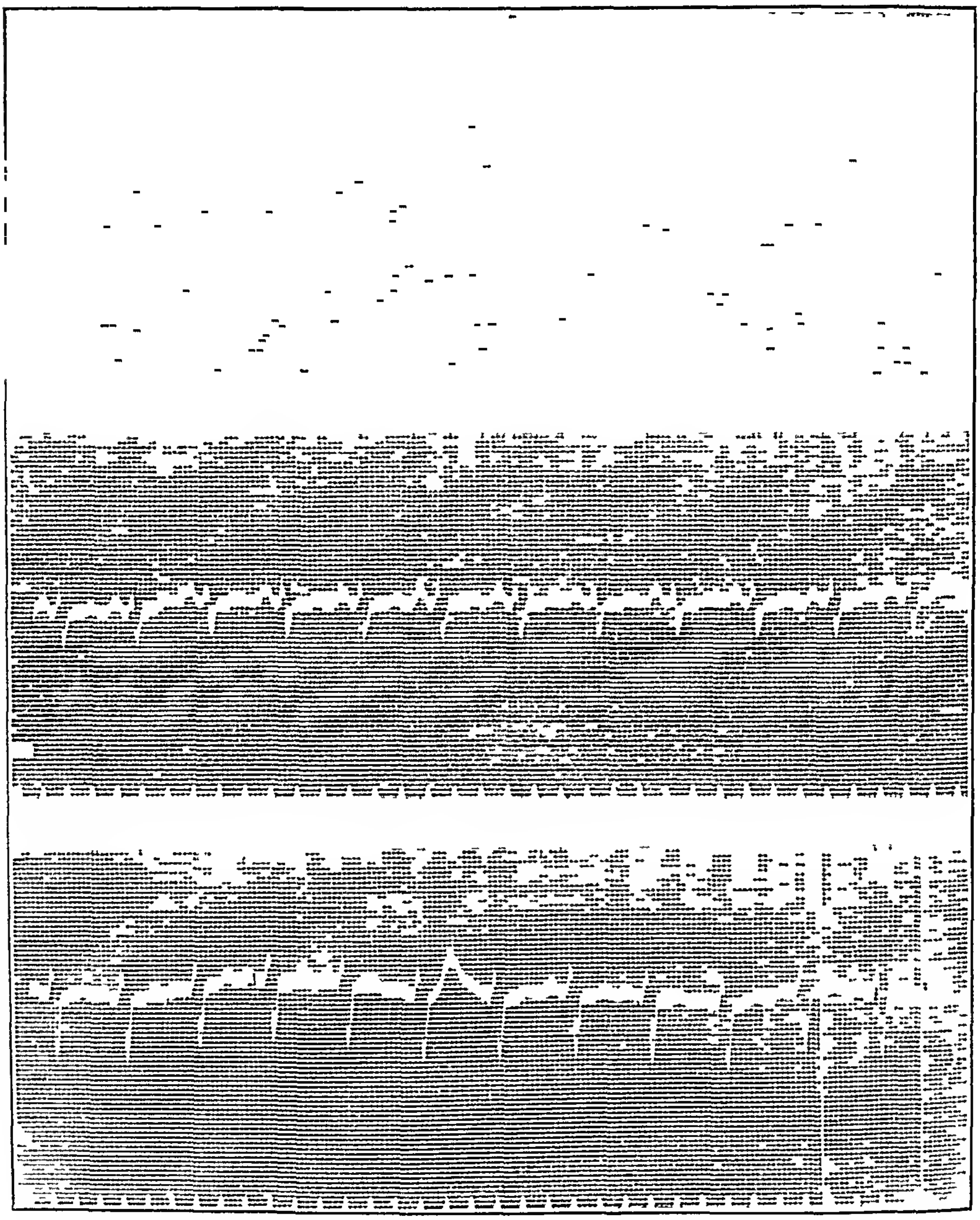

Fig 6—F N, Oct 28, 1916, 9 30 a m The heart now has a normal rhythm with a rate of 100 Large P-waves are present The ventricular complexes have greatly changed but still suggest some bundle effect Diagnosis left ventricular hypertrophy? or defective conduction of the right branch of the bundle of His?

Electrocardiograms—The electrocardiographic tracings (Fig 5) taken during a paroxysm and soon after admission to the hospital

show an unusual type of complex, not at all characteristic of paroxysmal auricular tachycardia No P-waves could be made out In Leads 2 and 3 the QRS interval is prolonged, as would be the case in ventricular extrasystoles or in right bundle block A rather high upward deflection beginning five-tenth second before the R-wave in

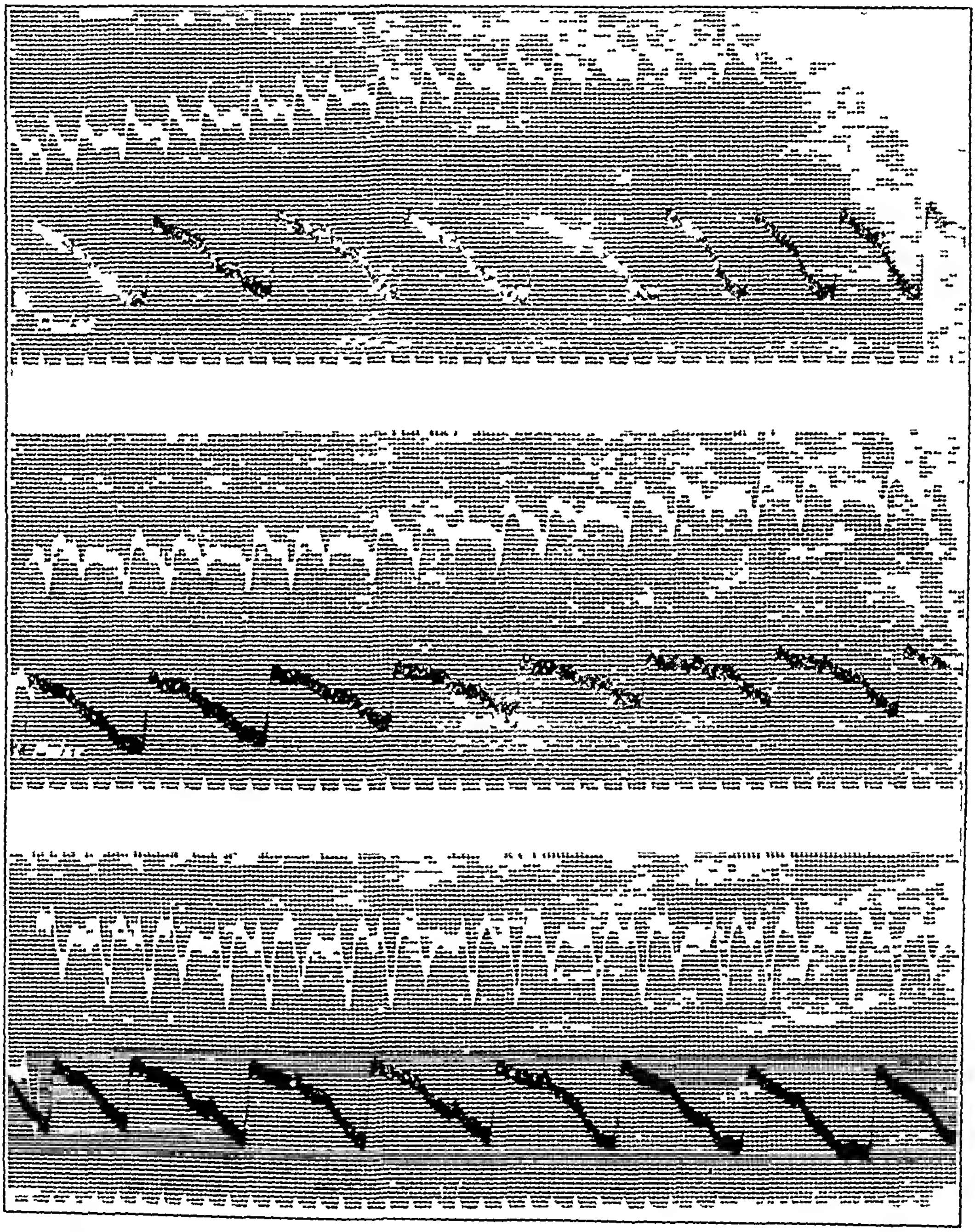

Fig 7—F N, Nov 3, 1916, 11 a m The heart is again in tachycardia with every second or third beat occurring prematurely The rate is 167 The P-waves cannot be made out Vagal stimulation has no effect on the rhythm Note the variation in the pulse with variation of the rhythm Soon after this tracing was taken the heart became regular at the same rate (167) The pulse tracing changed so that every beat was of constant size

all three leads may be simply a T-wave or it may be a T-wave with a superimposed P-wave In the downward deflection of the R-wave in Lead 2 is found a constant slight electrical variation which might also indicate a P-wave This can also be made out indistinctly in Lead 1, but it is not found in Lead 3 Comparison of Figure 5 with Figure 6 taken after the heart has resumed its normal rhythm shows that especially in Leads 2 and 3 the QRS complex still has some similarity to that of the rapid rhythm There is some suggestion of bundle defect, but the deflection in the downward stroke of the R-wave is now absent The P-R interval is here four-twenty-fifths second If, then, the P-waves in Figure 5 precede the R-waves by about five

Fig 8—F N, Nov 5, 1915, 10 30 a m There are many premature ventricular beats, and complexes similar to those in the tachycardia can be found One cannot with certainty locate P-waves occuring during the extrasystoles Diagnosis left ventricular hypertrophy, premature ventricular beats

twenty-fifths second they will be seen on the curve to coincide with the T-waves in Leads 2 and 3 In Lead 1 the position of the P-wave is more obscure

With the heart again in tachycardia and with every third beat coming prematurely as is shown in Figure 7, we are dealing with ectopic beats from two distinct sources — the first being identical with that found in Figure 5, the second being in the left or apical portion of the ventricle In these curves there is seen rather a suggestive similarity between the two types of ectopic complexes, which strengthens but far from confirms the suspicion that both types are of ventricular origin The curves of Figure 8, taken after the second

paroxysm had ceased, show in Leads 1 and 2 and also in Lead 3 (not reproduced) evidence of left cardiac hypertrophy They also show curves of premature ventricular beats arising from at least two foci, neither of which is identical with the possible focus discussed in Figure 5 Later, electrocardiograms all show a nearly normal electrocardiographic complex

It is impossible to determine definitely whether this patient has had an attack of paroxysmal auricular tachycardia in which there was present at the same time left ventricular hypertrophy and defective conduction in the His bundle, or whether he had an attack of true paroxysmal ventricular tachycardia The evidence, I believe, favors the first possibility

DISCUSSION

In the cases studied we have one instance of undoubted paroxysmal ventricular tachycardia and one in which the site of impulse formation cannot be definitely located, but may be in the ventricle and is again of the paroxysmal tachycardia type The interesting feature is that of eighteen cases of true paroxysmal tachycardia only two show electrocardiograms similar in character to those shown experimentally to be due to impulse formation within the ventricular walls All of the others are of auricular origin Isolated ventricular extrasystoles, supposed to be the result of a hyperirritable condition of an isolated portion of ventricular musculature, are clinically of frequent occurrence, being perhaps the most frequent cardiac arrhythmia recorded graphically outside of sinus arrhythmia Moreover, in view of the frequency of administration of digitalis in various chronic conditions, and in consideration of the well known action of the drug in increasing the muscular irritability, it seems contrary to expectation that runs of ventricular extrasystoles should be so rare

Considering this, we have reviewed 189 cases in the records of the medical service of the Peter Bent Brigham Hospital, among the diagnoses of which there was present in each case that of premature ventricular beats The majority of these cases showed additional cardiac disease and 118, or 63 per cent, received therapeutic doses of digitalis while in the hospital Of the 189 cases, but seven, or 4 per cent, showed two successive ventricular extrasystoles, among which one showed three in succession (This case was included in a series reported by Christian [9]) Two of the patients with duplicated extrasystoles received no digitalis, but one of these had severe cardiac damage and showed also bigeminy He died within two days after

9 Christian, Henry A Transient Auriculoventricular Dissociation, with Varying Ventricular Complexes Caused by Digitalis, The Archives Int Med, 1915, **16**, 341

admission All the other cases received some digitalis preparation Twenty-three cases, or 12 per cent, showed bigeminy by the electrocardiogram Four of these received no digitalis In a large proportion of these 189 cases digitalis was not administered until after the curves had been made, because the custom has been to take tracings in cardiac patients showing nothing very unusual, soon after admission, and to repeat only if there is some change But on subsequent tracings, when made, no increase in the number of successive extrasystoles appears Where subsequent tracings were not made there was no intimation of such a condition in the clinical notes It is safe to say that had such a condition occurred, it would have aroused suspicion and further electrocardiograms would have been made We may conclude, therefore, that digitalis in therapeutic doses in the majority of cases does not markedly increase the tendency to successive ventricular extrasystoles

The next question is, naturally, as to the effect of toxic doses of digitalis Of twenty cases having among their diagnoses the electrocardiographic diagnosis of digitalis intoxication, but two had two successive ventricular extrasystoles, and one more (previously referred to) had three in succession Bigeminy was rather frequent, trigeminy less so, but the most usual indication of digitalis intoxication was interference, to varying extent, with conduction from the auricles to the ventricles Auricular flutter and fibrillation were also noted in a case with digitalis intoxication, but occurring in a moribund heart

SUMMARY

In eighteen cases of paroxysmal tachycardia only two, which are here reported in detail, showed a site of impulse formation elsewhere than in the auricles Study of the literature points to the infrequency of cases of paroxysmal tachycardia of ventricular origin To those already reported two are added Digitalis may be an exciting cause in the production of the condition, but there must be some other predisposing factor such as ventricular hyperirritability from impaired blood supply or from some other cause

PHARMACODYNAMIC EXAMINATION OF THE VEGETATIVE NERVOUS SYSTEM IN TYPHOID FEVER

A CONTRIBUTION TO THE PROBLEM OF BRADYCARDIA *†

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The hypothesis of vagotonia and sympathicotonia, established by Eppinger and Hess,[1] gave a clearer explanation of diseases whose pathology was heretofore not quite obvious, thereby opening a new way to diagnosis and treatment

According to their orginal opinion, there exists an equilibrium between the sympathetic and autonomic (parasympathetic) nervous systems, through which the inner organs and the involuntary apparatus perform their functions smoothly When this equilibrium is once disturbed, however, from any cause, the action of one becomes predominant, and various pathologic conditions arise By means of drugs which act especially on the vegetative nervous system, this disturbance becomes so marked that it greatly facilitates the diagnosis

This disturbance is due to the abnormal tonus of either the sympathetic or autonomic nervous system, in other words, everybody who is sensitive to atropin and pilocarpin is not sensitive to epinephrin, and vice versa They named the former condition vagotonia, the latter sympathicotonia They did not observe any one who was sensitive to both groups (atropin-pilocarpin and epinephrin), at least in the doses they used

Later it became necessary to make some corrections, as their original opinion seemed to be too dogmatic, for there were some individuals who were sensitive to all three drugs

Even Eppinger and Hess themselves, together with Potzl,[2] observed such a condition in some psychoses Falta, Neuburgh and Nobel[3] observed some persons who were sensitive to both epinephrin and pilocarpin

Since this hypothesis was established, many investigators have tested the functions of the vegetative nervous system in their clinics and published their results Petrén and Thorling,[4] in their observa-

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1 Eppinger and Hess Ztschr f klin Med, 1909, **67,** 345, *ibid,* 1909, **68,** 205, *ibid,* 1909, **68,** 231

2 Potzl, Eppinger and Hess Wien klin Wchnschr, 1910, p 1381

3 Falta, Neuburgh and Nobel Ztschr f klin Med, 1911, **72,** 97

4 Petrén and Thorling Ztschr f klin Med, 1911, **73,** 27

tions on ulcer of the stomach, found numerous cases of vagotonia, but very few of sympathicotonia This coincided with what Eppinger and Hess had reported At the same time, however, they could not deny the existence of individuals who were sensitive to epinephrin and pilocarpin, so they concluded that a man who is sensitive to atropin and pilocarpin is not entirely nonsensitive to epinephrin, and that atropin and pilocarpin do not always act in parallel They emphasized the difference between the elevation of tonus and that of irritability When the tonus is elevated, it must be sensitive to both kinds of drugs, the paralyzing and the stimulating Bauer[5] examined many patients who were considered by Eppinger and Hess to be vagotonic and sympathicotonic, and found that many of them were sensitive to both epinephrin and pilocarpin In cases which were supposed to be of sympathicotonia, he found strong reaction for pilocarpin Lehmann[6] examined 100 persons, including a variety of patients and some healthy controls, and found that 95 per cent of those sensitive to epinephrin were also sensitive to pilocarpin On the other hand, pilocarpin and atropin did not act in parallel Thus they both doubted the hypothesis of Eppinger and Hess

Besides these, Deutsch and Hoffmann[7] utilized this test in pulmonary tuberculosis, Wentges,[8] Ando,[9] as well as Hopkins,[10] in functional nervous diseases, Thies[11] in diseases of the bile duct

Molchanoff and Lebedeff[12] tried this test in ten children with scarlet fever, during the period of recovery, and recorded the majority of these cases as of distinct vagotonia

No one has as yet, however, undertaken such a test on typhoid fever This fact alone awakes some interest In typhoid fever, as is well known, there sometimes exists striking bradycardia, even in the fever period, for which there is no satisfactory explanation Our work is an attempt at a solution of this problem through the hypothesis of Eppinger and Hess Our investigation, in fact, started with this point in view

Material for Experiments—As material we used typhoid fever patients, including seven cases of paratyphoid B, who were admitted to the Kyoto Infectious Disease Hospital, all bacteriologically and serologically proved Up to the time of examination no complication

5 Bauer Deutsch Arch f klin Med, 1912, **107,** 39
6 Lehmann Ztschr f klin Med, 1914, **81,** 52
7 Deutsch and Hoffmann Wien klin Wchnschr, 1913, p 569
8 Wentges Deutsch Arch f klin Med, 1914, **113,** 607
9 Ando Kyoto Igaku Zassi, 1916, **13,** No 1
10 Hopkins The Archives Int Med, 1913, **22,** 556
11 Thies Mitt a d Grenzgeb d Med u Chir, 1914, **27,** 389
12 Molchanoff and Lebedeff Russk Vrach, cited in Jour Am Med Assn, 1916 **67,** 475

had set in All were more than 14 years old We avoided patients who were in excited states At first we chose patients who had relative bradycardia, as they were the most suitable for our purpose Afterwards, however, we also tested as controls patients who had no bradycardia, and some with tachycardia

Method of Experiment—For the pharmacodynamic examination we used atropin, pilocarpin and epinephrin It is necessary to make a few remarks concerning the doses used Eppinger and Hess administered hypodermically atropin, 0 001 gm, to men, 0 00075 to women, epinephrin 0 001 gm for men, 0 00075 for women, and pilocarpin 0 01 gm for men, 0 0075 for women Three hours before the injection of epinephrin 100 gm of glucose were given per os Petrén and Thorling used almost the same doses as Eppinger and Hess Bauer gave relatively small doses, namely, pilocarpin 0 007 gm, epinephrin 0 0007, giving 100 gm of glucose three hours before the injection, and of atropin 0 0005 gm Wentges used the same as Bauer Lehmann almost the same as Eppinger and Hess

To criticize such a new hypothesis it is best to follow the original method, therefore we adopted the doses of Eppinger and Hess atropin 0 001 gm, epinephrin 0 001 gm, subcutaneously According to Burgusch and Schittenhelm,[13] in cases in which 0 001 epinephrin was injected following 100 gm of glucose per os, glucose could be found even in the urine of the healthy So we tested glycosuria qualitatively without giving glucose previously As intestinal hemorrhages may take place by increased peristalsis, we used 0 007 gm pilocarpin instead of 0 01 gm (Eppinger and Hess)

After injection of atropin, rate of pulse, degree of thirst and palpitation were observed for from one to one and one-half hours After injection of epinephrin, pulse, blood pressure (by Riva-Rocci), body temperature (axillary), respiration, tremor, palpitation and pallor were observed for one hour, and glycosuria was tested for (Trommer and Nylander) After injection of pilocarpin, pulse, salivation, sweating and gastro-intestinal disturbances were observed for one hour

Besides the pharmacodynamic test, respiratory arrhythmia, Aschner's bulbus phenomenon and dermographia were observed, but Tschermack's press trial was not tested

All patients in the fever period were tested between the first and third weeks, and observed lying absolutely quiet on their backs throughout the procedure Examinations were not begun until the pulse showed a constant rate, so that the psychic influence was avoided

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13 Burgusch and Schittenhelm Technik d speciel klin Untersuchungsmethoden, Part 2, p 896

We injected, in turn, atropin, epinephrin and pilocarpin, with an interval of from one to two days between them

Standard for Test—The standard of criticism, whether the result of the pharmacodynamic test is positive or negative, must be shown It is a self-evident fact that the drugs we used are poisons and therefore have some action even on the healthy who have no abnormal tonus or irritability in their vegetative nervous systems When reaction is very strong in comparison to doses, there is no doubt that the result is positive

Atropin When 0 001 gm atropin was injected, the disturbance of salivation, mydriasis and decreased tonus of stomach and intestine would be expected theoretically, but these symptoms are not constant, consequently, we must rely on a change of heart function (Burgusch and Schittenhelm[13]) Eppinger and Hess demonstrated double increase of pulse rate, sometimes accompanied by palpitation, as a strong atropin action Petrén and Thorling counted as positive those who had, in addition to thirst or palpitation, an increase of more than 20 in pulse rate Lehmann considered the test as positive when there was an increase of 30 in the pulse rate, accompanied by thirst or palpitation, or when it was the only symptom an increase of pulse rate of more than 30 We counted it positive, as did Petrén and Thorling, when there was an increase of more than 20 in pulse rate, expressed by +, when more than 30 by ++, secondly, thirst and palpitation were taken into consideration When the increase was 17 or 18 beats, if accompanied by increased thirst or palpitation, it was counted as positive, if not, as negative

Epinephrin When 0 001 epinephrin was administered, even in the healthy, after from five to ten minutes, palpitation, pallor, slight tremor, increase of pulse rate and elevation of blood pressure could be seen (Burgusch and Schittenhelm) Eppinger and Hess described excretion of more than 5 gm glucose (100 gm glucose were given before), double the quantity of urine, one third increase in pulse rate and increase of reflexes as a strong reaction to epinephrin Petrén and Thorling, and Bauer did not show the standard clearly Lehmann counted as positive more than 30 increase of pulse rate, more than 3 gm glucose in urine (100 gm glucose were given before) and marked tremor We counted positive more than 20 increase of pulse rate, more than 20 mm Hg increase of blood pressure, marked tremor, considerable palpitation and glycosuria (no previous administration of glucose) When more than two symptoms were observed and they were strong, we marked them + or ++, according to their strength When the only symptom was increase of pulse rate or elevation of blood pressure, we counted it as negative unless the increase was more than 30 Glycosuria alone, on the contrary, counted as positive

Pilocarpin When 0 007 pilocarpin was injected, even in the healthy, after from five to seven minutes, salivation and sweating were noticed The pulse ought to be decreased theoretically, but was found increased practically (Burgusch and Schittenhelm) Eppinger and Hess considered as a strong pilocarpin reaction, profuse salivation and profuse sweating Lehmann laid chief stress on salivation, less on sweating and other symptoms He put no value on increase of pulse rate We considered sweating and salivation, when profuse and of long duration, as positive Gastro-intestinal symptoms were also looked on as significant When either sweating or salivation alone existed, we considered it negative, unless accompanied by gastric and intestinal symptoms

EXPERIMENTS

Atropin The action of atropin was examined in forty-six cases A noteworthy phenomenon after injection was the paradoxical action, namely, from five to fifteen minutes after injection the pulse rate decreased The pulse decrease was 3 in four cases, 4 in three cases, 5 in four cases, 6 in three cases and 7 in one case After this decrease the pulse rate sometimes increased remarkably, but at others remained in the decreased condition The most remarkable was Case 5, which showed a decrease of 17 in pulse rate after injection, accompanied by arrhythmia, and Aschner's bulbus phenomenon was also observed Bauer had already described this paradoxical phenomenon, accompanied also by arrhythmia, only when small doses were given (0 0001 to 0 0002 of atropin), and that both bradycardia and arrhythmia disappeared when relatively large doses were given (0 0005) We, however, observed such a phenomenon by injecting 0 001, the same as Lehmann A striking increase of pulse rate was seen in the following cases 49 in Case 46, 39 in Case 14, 38 in Case 9, 32 in Case 13, 31 in Case 15 and 30 in Case 8, increase between 20 and 29 in six cases, 10 and 19 in fourteen cases and 0 and 9 in nine cases It must also be noticed that increase of more than 30 pulse rate all occurred in youths (aged from 14 to 19) Eppinger and Hess said that the vagotonic condition was observed mostly in youths

Lehmann also wrote that youth is sensitive to atropin We show the relation in Table 1 to make the matter clearer

TABLE 1—RELATION OF AGE AND SENSITIVENESS TO ATROPIN

Age	Cases Observed	Positive Reaction
14 to 19	16	10
20 to 29	12	5
30 to 39	13	3
40 to 67	5	3
Total	46	21

Here we must record the investigation published by Marris,[14] who reports that in practically all cases of the typhoid group during some period of the infection (mostly the second week), the rate of the heart cannot be accelerated by atropin as it can be in normal people and those suffering from other diseases, and uses this reaction as a means of diagnosis

In our forty-six cases of typhoid fever (including seven cases of paratyphoid B), however, atropin was quite active, accelerating the rate of pulse, especially in cases of bradycardia As all our cases were serologically and bacteriologically controlled, the diagnosis was undoubtedly correct

All cases were tested during the fever period (between the sixth and the twenty-third day), and every possible precaution was also taken during the procedure

The conditions were apparently the same as in the cases of Marris, notwithstanding that our results were evidently not in accord with his findings, for which we can give no satisfactory explanation at present

Epinephrin In 46 cases the action of epinephrin was examined Epinephrin injection always accelerated the pulse, and no paradoxical phenomenon was observed Remarkable increases were noticed as follows 56 in Case 46, 52 in Case 40, 42 in Case 11, 35 in Case 10, from 20 to 29 in nineteen cases, from 10 to 19 in sixteen cases and from 2 to 9 in seven cases The blood pressure was also always elevated There were increases of 41 mm in Case 36, 37 in Case 7, from 20 to 30 in thirteen cases, from 10 to 19 in nineteen cases and from 0 to 9 in ten cases The respirations also accelerated after injection, as Bauer observed increases of 11 in one case, 8 in three cases, 6 in three cases, 5 in five cases and 4 in eight cases

In regard to temperature, any change that occurs immediately, namely, from 5 to 10 minutes after the injection, must be due to the epinephrin action Increase of 0 8 C in 1 case, 0 7 in 1 case, 0 6 in 1 case, 0 5 in 3 cases and 0 4 in 2 cases were observed Epinephrin glycosuria was observed in 8 cases out of 45, tremor in 18 cases, mostly in the hand, palpitation in 15 cases, general lassitude, nausea and headache in some cases

As Bauer and Lehmann observed, epinephrin does not act the same on every person They called this condition dissociation of drug action This dissociation was evident also in our cases Table 2 shows the facts clearly

14 Marris Brit Med Jour, 1916, 2, 717

TABLE 2—Dissociation of Drug Action After Epinephrin

Cases	
1	Glycosuria, elevation* of blood pressure, increase of pulse rate
1	Glycosuria, elevation of blood pressure
3	Glycosuria, increase of pulse rate
3	Glycosuria
8	Elevation of blood pressure, increase of pulse rate
5	Elevation of blood pressure
10	Increase of pulse rate

* By increase or elevation we mean more than 20 in pulse rate or more than 20 mm of mercury in blood pressure, respectively

As the table shows, three symptoms were observed in one case only

Eppinger and Hess noticed that sympathicotonia is often seen in old people, while Lehmann, on the contrary, stated that youth is sensitive to epinephrin In our experiments we noticed no relation between sensitiveness to epinephrin and age, as shown by Table 3

TABLE 3—Relation of Age and Sensitiveness to Epinephrin

Age	Cases Observed	Positive Reaction
14 to 19	16	9
20 to 29	12	6
30 to 39	13	9
40 to 67	5	2
Total	46	26

Pilocarpin Pilocarpin was tested in thirty-eight cases Pilocarpin decreases the pulse rate in animal experiments, but on the human body, on the contrary, it has no such effect (Eppinger and Hess) Bauer and Lehmann even maintained that it caused an increase

It must be noticed in Case 9, in which, after injection of 0 007 pilocarpin, besides profuse salivation and sweating, the pulse rate decreased 14 within five minutes and returned to normal after nineteen minutes Arrhythmia was observed at the same time This fact, which nobody has as yet described, is very significant and interesting In all other cases except Case 9 the pulse rate increased after injection increases of 42 in Case 15, 37 in Case 13, 36 in Case 3, 33 in Case 11, 30 in Case 14, and from 20 to 29 in eleven cases, from 10 to 19 in fifteen cases and from 2 to 9 in nine cases

Gastro-intestinal symptoms were seldom observed nausea in two cases, vomiting in one case, gurgling of intestine in two cases and singultus in two cases

Salivation and sweating began in sensitive cases five minutes after injection and lasted one hour They almost always go hand in hand, however, there are some cases in which there is profuse salivation with very little sweating (Cases 27 and 38), and cases in which there is profuse sweating with no salivation (Cases 23, 26 and 36)

Thus, dissociation was observed even in pilocarpin action, as Bauer had already noted, but not so remarkable as in the case of epinephrin

There is no relation between the action of pilocarpin and age Table 4 shows the fact

TABLE 4—Showing Absence of Relation Between Age and Action of Pilocarpin

Age	Cases Observed	Positive Reaction
14 to 19	13	11
20 to 29	10	6
30 to 39	11	7
40 to 67	4	3
Total	38	27

DISCUSSION

The pharmacodynamic test of the vegetative nervous system in the fever period of typhoid fever was examined in forty-six cases in all

In thirty-eight of them, atropin, pilocarpin and epinephrin were tested, and in eight cases atropin and epinephrin The results we obtained from the thirty-eight cases may be classified as in Table 5

TABLE 5—Reactions to Atropin, Pilocarpin and Epinephrin

Reactions	Group	Cases Observed
Sensitive to atropin and pilocarpin, nonsensitive to epinephrin	1	14
Sensitive to epinephrin, nonsensitive to atropin and pilocarpin	2	11
Sensitive to atropin, pilocarpin and epinephrin	3	3
Sensitive to pilocarpin and epinephrin	4	7
Sensitive to pilocarpin	5	3

The first group in Table 5 corresponds to vagotonia, the second to sympathicotonia according to Eppinger and Hess The third group is thought to be sympathetic and autonomic in elevated tonus, as once observed by Eppinger, Hess and Potzl in cases of psychosis The fourth group is the condition of heightened irritability of sympathetic and autonomic as often observed by Bauer and Lehmann The fifth group is considered to be autonomic in elevated irritability

The principal objections which were made by Petrén and Thorling, Bauer, and Lehmann to the opinion of Eppinger and Hess consist of the following two points first, there are cases which are sensitive to both pilocarpin and epinephrin, second, atropin and pilocarpin do not act in parallel Some of our experiments also confirmed this objection, namely, Group 4 shows sensibility to both epinephrin and pilocarpin, and Groups 4 and 5 show no parallelism between the action of atropin and pilocarpin

We cannot, however, entirely agree with those who give up thereby the significant hypothesis of Eppinger and Hess Quite a number of cases in such a state, namely, vagotonia and sympathicotonia, were confirmed by us

Now let us assume the formula which was given by Liebermeister,[15] of counting the pulse rate from the body temperature Rate of pulse $= 80 + 8 \times (T - 37)$, T is the number read on the thermometer

By means of this formula, we obtain the pulse rate corresponding to body temperature at the time of examination, and comparing this number with the true pulse rate, we know the relative bradycardia, that is, the more difference there is between pulse calculated and observed, the more pronounced the bradycardia

Arranging our thirty-eight cases in order of relative bradycardia (Table 6), the following significant and important fact is found, namely, the cases of Group 1 (vagotonia) are placed in the upper spaces of the table, while those of Group 2 (sympathicotonia) are placed in the lower spaces In other words, in cases of typhoid fever, a patient who has a significant bradycardia is mostly sensitive to atropin and pilocarpin, and one who has no bradycardia is mostly sensitive to epinephrin Only those who have marked bradycardia are especially sensitive to atropin

Supposing the bradycardia in typhoid fever were due to loss of equilibrium between sympathetic and autonomic, we may consider several possibilities, for instance, such a condition may be expected in abnormally elevated tonus of autonomic, or diminished tonus of sympathetic, or by stimulating autonomic only The action of typhoid toxin for sympathetic and autonomic is not quite obvious According to our experiments, however, we proved that 60 per cent of marked bradycardia in typhoid fever is in the state of vagotonia, thus the so-called vagotonia may be considered as one cause of typhoid bradycardia

Wenckebach[16] described recently in his book two kinds of bradycardia, one, cardial bradycardia, which is not accompanied by arrhythmia, the other, vagal bradycardia, which is always accompanied by arrhythmia He also mentioned one case of bradycardia in typhoid fever which was of a vagal nature, and Pierret and Dartevelle[17] also found a similar case Though their observations were made from the standpoint of arrhythmia, and ours from pharmacodynamic test, the results unexpectedly coincided

15 Liebermeister Cited in Daten u Tabellen, Vierordt, 1893, p 156

16 Wenckebach Die unregelmassige Hertztatigkeit u ihre klin Bedeutung, 1914 p 192

17 Pierret and Dartevelle Cited in Wenckebach (Footnote 16)

TABLE 6—SUMMARY OF AUTHORS' OBSERVATIONS

Group	Number of Cases	Age	Sex	Body Temperature, C	Pulse Observed	Pulse Calculated	Relative Bradycardia	Atropin Reaction	Epinephrin Reaction	Pilocarpin Reaction	Deaths
3	14*	15	♂	38 0	56	88	32	++	+++	+	
1	9	16	♂	39 3	67	98	30	++	—	++	
1	4	68	♀	39 1	68	97	29	++	—	++	
4	11	33	♂	39 0	71	96	25	—	+++	+	
1	15	16	♂	39 0	73	96	23	++	—	++	
1	5	20	♂	39 4	77	99	22	++	±	++	
1	2	19	♂	39 6	80	101	21	+	—	+++	
2	25	21	♂	38 9	74	95	21	±	+	—	-
1	8	14	♂	39 7	85	102	17	++	—	++	
4	10	44	♂	38 3	73	90	17	—	+	+	
1	32	35	♂	38 6	79	93	14	+	±	+	
4	37	15	♂	39 4	85	99	14	—	+	+	
2	30	21	♂	39 1	83	97	14	—	+	—	-
1	17	22	♂	39 3	86	99	13	+	—	++	
1	3	15	♂	39 0	86	96	10	+	—	+	
1	12	24	♂	39 1	87	97	10	+	—	+	
1	13*	16	♂	37 8	76	86	10	++	±	+	
1	31*	23	♂	40 3	98	107	9	+	—	+	
1	19	40	♂	39 1	88	97	9	+	—	+	
3	24	31	♂	38 7	85	94	9	+	++	+	
1	1	26	♀	38 5	84	92	8	+	±	++	
4	6	32	♂	39 9	96	102	8	—	+	+	
2	36*	34	♂	38 9	88	96	8	—	++	±	
4	16	20	♂	39 3	92	98	6	±	+	+	
2	27	36	♂	39 5	94	100	6	—	++	—	-
2	26	24	♂	39 3	93	98	6	—	+	—	-
2	23	48	♀	39 7	98	102	4	—	+	—	
4	7	19	♂	38 7	90	94	4	—	++	++	
2	21	17	♂	39 2	95	98	3	—	+	—	
3	18*	16	♂	39 5	100	100	0	+	+	+	
5	20	26	♀	38 3	90	90	0	—	—	+	
2	29	18	♂	39 5	104	100	4†	—	+	—	
5	28*	15	♂	39 9	108	103	5†	—	—	+	
2	38	34	♀	39 5	106	100	6†	—	++	±	-
2	33	21	♀	39 5	106	100	6†	—	+	—	
2	22	14	♀	39 2	108	98	10†	—	+	—	
4	34	38	♀	38 8	104	94	10†	—	+	+	
5	35	32	♂	39 1	107	97	10†	—	±	++	

* Cases of Paratyphus B   † Tachycardia

Another interesting fact is that our five fatal cases out of thirty-eight were all in the state of sympathicotonia, and one incurable patient out of eight tested for atropin and epinephrin reactions, was sensitive to epinephrin and nonsensitive to atropin

It is a well known fact that in typhoid fever a rapid pulse signifies a doubtful prognosis This fact has been ascertained by long experience and coincides with the result of our investigation Furthermore, we already knew that the state of sympathicotonia is often seen in patients with a rapid pulse We may also say that even in cases of bradycardia nonsensitive to atropin and pilocarpin, and sensitive to epinephrin, the prognosis is not good (Cases 25 and 30) This fact, which must be confirmed by repeated experiments, may be of some significance in establishing the prognosis of typhoid fever Consequently, the examination of the functions of the vegetative nervous system in typhoid fever is indispensable

SUMMARY

1 In typhoid cases, atropin acts strongly on those patients who have marked bradycardia, but has almost no effect on those who have no bradycardia Increase of pulse rate is the most significant atropin action, then comes increase of thirst, and lastly palpitation In only one case the remarkable paradoxical phenomenon, decrease of 17 in pulse rate, accompanied by arrhythmia, was observed

2 After injection of epinephrin, increase of pulse rate, elevation of blood pressure, acceleration of respiration and elevation of body temperature were observed in many cases Tremor and glycosuria were often observed, but palpitation, nausea, and headache seldom

So-called dissociation of epinephrin action was observed even in cases of typhoid fever

3 In the majority of cases salivation and sweating were observed after pilocarpin injection, besides nausea, vomiting and singultus In only one case were we able to find a decrease of 14 in the pulse rate, accompanied by arrhythmia This fact has never been noticed by anybody up to this time Dissociation may be seen after pilocarpin in typhoid fever, but not so marked as after epinephrin

4 According to our experiments, though youth is sensitive to atropin, no relation is to be seen between the action of epinephrin and age or pilocarpin and age

5 Examining the function of the vegetative nervous system in 38 cases of typhoid fever, we found 14 cases which corresponded to vagotonia, 11 cases which corresponded to sympathicotonia, 3 cases which

were sensitive to all three drugs, 7 cases which were sensitive to pilocarpin and epinephrin, and 3 cases which were sensitive only to pilocarpin

6 Though the cases supporting the objections made by Bauer and Lehmann are not rare, still in the majority of typhoid fever cases the state of vagotonia or sympathicotonia exists, which fact conforms with the opinion of Eppinger and Hess

7 In the cases with marked bradycardia, the state of vagotonia was often observed, while in those with no bradycardia, sympathicotonia was often observed

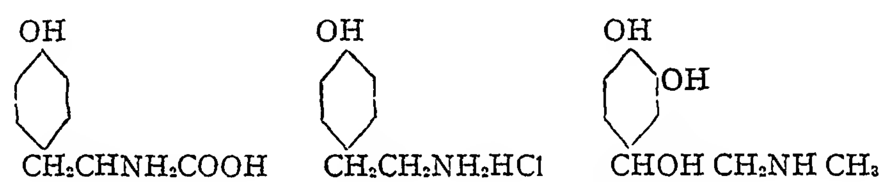
8 The state of vagotonia may be one explanation for bradycardia in typhoid fever

9 The deaths in our cases were all in the condition of sympathicotonia This fact may form the basis for establishing a prognosis in typhoid fever

THE ACTION OF TYRAMIN ON THE CIRCULATION OF MAN *

ALBION WALTER HEWLETT, M D
SAN FRANCISCO

Tyramin is a hydrochloric acid salt of parahydroxyphenylethylamin The latter is the most active blood pressure raising constituent in watery extracts of ergot[1] It has been isolated from putrid meat[2] and from other decomposing organic substances Here it appears to be formed by the action of bacterial ferments on tyrosin, one of the common amino-acid building stones of the protein molecule The structural relationship of tyramin to tyrosin and to the physiologically related epinephrin is shown in the following structural formula



Tyrosin — Tyramin — Epinephrin

The action of tyramin on the circulation of animals was studied by Dale and Dixon,[3] who found that the intravenous injection of 1 mg into the cat or into other laboratory animals was followed by a sudden and marked rise of arterial blood pressure, reminiscent of that produced by epinephrin As compared with the latter, however, the blood pressure changes showed a longer latent period, the rise to the maximum was less sudden and the decline to the original level was more gradual Cardiometer tracings taken by these authors showed that the rise of blood pressure was associated with an increase in the amplitude of the ventricular beats This occurred even when the slowing of the heart was eliminated by section of the vagus nerves or by their functional exclusion with atropin Apparently, therefore, the heightened blood pressure was due in part to an increased output from the heart

Dale and Dixon also found that tyramin constricted the systemic blood vessels Volume tracings from the dog's ear, from a loop of

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* From the Division of Medicine, Stanford Medical School

1 Barger, G, and Dale, H H The Water-Soluble Active Principles of Ergot, Proc Physiol Soc, May 15, 1909, Jour Physiol, 1909, **38**, 77

2 Barger, G, and Wampole, G S Isolation of the Pressor Principles of Putrid Meat, Jour Physiol, 1909, **38**, 343

3 Dale, H H, and Dixon W E The Action of Pressor Amines Produced by Putrefaction, Jour Physiol, 1909, **39**, 25

the cat's intestine and from the hind extremity showed a shrinkage of these organs when the drug was injected Furthermore, the addition of tyramin to the fluid used in perfusing the cat's hind limb and the dog's small intestine caused a marked slowing of the flow through these organs The pulmonary vessels, on the other hand, were not constricted by tyramin From these observations it would appear that the rise of blood pressure produced by the intravenous injection of tyramin into laboratory animals was due not only to an increased output from the heart, but also to a constriction of the peripheral blood vessels

Tyramin, like epinephrin, appears to act only on such muscle fibers and gland cells as receive a sympathetic nerve supply According to Dale and Dixon, the effects produced on these structures, whether stimulating or inhibiting, are comparable to those produced by excitation of the sympathetic nerves themselves Although the action of tyramin resembles that of epinephrin in this particular, the two actions are not identical Not only is tyramin much less active, being about one twentieth as powerful when judged by its pressor effects, but qualitative differences between the two drugs also exist Thus Baehr and Pick[4] found that while epinephrin caused a dilatation of the bronchi, tyramin caused a constriction With respect to the blood vessels, it has been noted that epinephrin produces a much greater local effect Thus Sollmann and Pilcher[5] found that the application of epinephrin to slight cutaneous abrasions caused marked local pallor, whereas tyramin was without effect Furthermore, tyramin has no value as a local hemostatic The constriction of the blood vessels about subcutaneous or intramuscular injections of epinephrin interfere with its absorption into the general circulation, and this is believed to account for the fact that such injections rarely produce the marked rises of blood pressure that follow intravenous administration of epinephrin On the other hand, tyramin with its less marked local effect, usually causes a striking elevation of the blood pressure when injected subcutaneously

EFFECT ON THE BLOOD PRESSURE AND PULSE RATE OF MAN

The effect of tyramin on the circulation of man was tested by Dale and Dixon, one of whom took 10 mg of the drug by mouth The moderate rise of systolic pressure which was observed in this experiment was probably due to some cause other than the drug given, for

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4 Baehr, G, and Pick E P Pharmakologische Studien an der Bronchialmuskulatur der uberlebenden Meerschweinchenlunge, Arch f exper Path u Pharmakol, 1913, **74,** 41

5 Sollmann, T and Pilcher, J D Endermic Reactions, Jour Pharm and Exper Therap, 1917 **9,** 309

Clark[6] showed subsequently that much larger doses — up to 200 mg within forty minutes — when given by mouth, produced no striking effect on the blood pressure If, however, tyramin were injected into man subcutaneously, it produced, in most instances, unmistakable circulatory effects Clark,[6] Hoyt,[7] and Watson,[8] each of whom studied the effect of subcutaneous injections on the blood pressure of man, found that tyramin usually caused a marked elevation of the systolic blood pressure This rise usually began within a few (two to ten) minutes, proceeded rapidly to its maximum and then fell somewhat more slowly to the original level The whole reaction occupied a period of fifteen to thirty minutes or more In order to produce an appreciable rise of pressure, 20 mg must ordinarily be injected Larger doses (60 to 80 mg) may cause very considerable elevations of pressure Watson,[8] who recorded the diastolic as well as the systolic pressure, found that the former was not affected by the drug, the heightened systolic pressure being due entirely to an increase in the pressure amplitude or pulse pressure When the systolic blood pressure rose, the pulse rate usually fell, presumably because the heightened blood pressure caused a vagus inhibition of the heart

In the present series of observations tyramin was administered subcutaneously in doses of from 40 to 80 mg , the usual dose being 60 mg The resultant changes in the systolic blood pressure and the pulse rate were similar to those described by the authors just cited In most instances the injection was followed within a few minutes by a striking rise in the systolic blood pressure and by a slowing of the pulse Illustrative curves are shown in Figure 1 From this figure it may be seen that the rise in systolic pressure began within five minutes after the injection, that the maximum elevation usually occurred within ten minutes after the injection, and that the blood pressure had usually returned to the normal in from twenty to thirty minutes Although Watson stated that the diastolic pressure was not affected by the drug, our observations indicate that in the doses given there was usually a slight but definite rise in the diastolic pressure This, however, was very much less than the rise in systolic blood pressure, so that there was a marked increase in the pulse pressure It is noteworthy also that the vascular sounds heard during the auscultatory determinations of blood pressure became much louder at the height of the tyramin action

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6 Clark, A The Clinical Application of Ergotamine, Biochem Jour , 1910-1911, **5**, 236

7 Hoyt, D M The Therapeutic Application of P Hydroxyphenylethylamin (Tyramine) , an Active Principle of Ergot, Am Jour Med Sc , 1912, **144**, 76

8 Watson, A Observations on the Value of Drugs as Blood Pressure Elevators, Practitioner, London, 1915, **94**, 566

The foregoing changes in the systolic blood pressure occurred in almost every instance when tyramin was injected in doses of 40 mg or more (Tables 1 and 2) Yet no very definite relation existed between the rise of pressure and the dose of drug administered In two persons, indeed, no rise of systolic pressure was observed The cause of such variations in the effect of the drug is not certain Aside from variations in individual susceptibility, the rate of absorption from the site of injection probably played a considerable rôle in

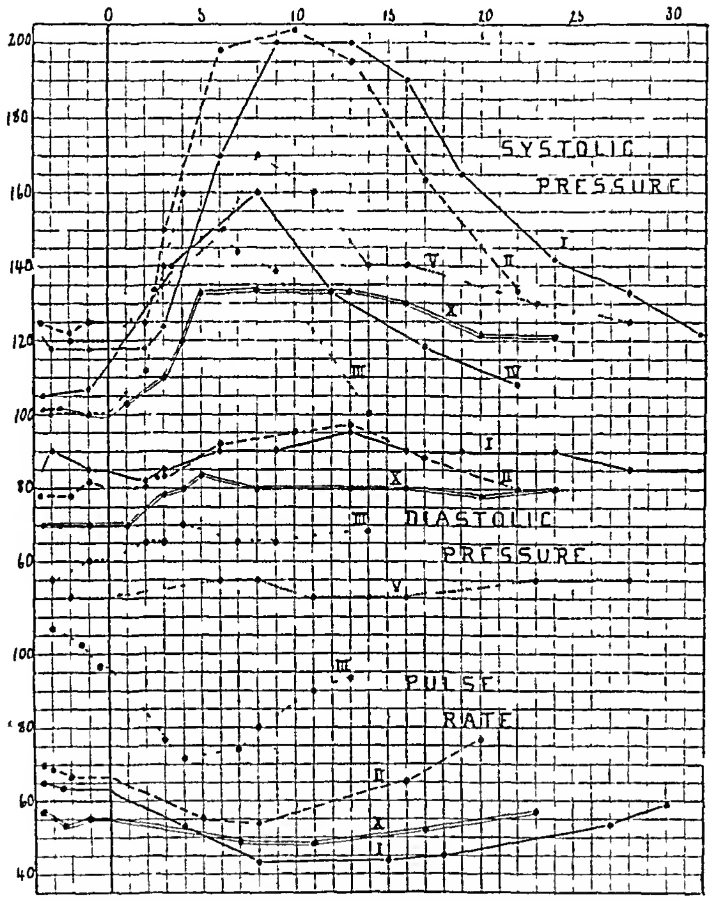

Fig 1—Chart showing the effect of tyramin on the systolic and diastolic blood pressure and on the pulse rate The Roman numerals correspond to the cases in Table 1

determining the intensity of the reaction Clark stated that when injections were given into the arm or forearm little general reaction followed, and he recommended that injections be given into the loose tissues about the clavicles In one of our tests without reaction a lump formed at the site of the injection in the forearm Following Clark's suggestion, therefore, most of the remaining injections were given into the loose subcutaneous tissues beneath the clavicle

Any marked rise of pressure was, as a rule, accompanied by a slowing of the pulse similar to that reported by others who have studied the clinical effects of the drug From Dale and Dixon's animal experiments this appears to result from vagus stimulation by the heightened blood pressure In two instances the pulse rate increased during the action of the drug One of these patients (No 13) had exophthalmic goiter and the pulse rate increased from 75 to a maximum of 84 The other patient (No 16) showed extrasystoles before the administration This irregularity became more pronounced and at the same time the sinus rate was accelerated (Fig 6) In the remaining tests any marked rise of systolic pressure was accompanied by a definite slowing of the heart rate, which disappeared as the pressure fell to normal

TABLE 1—Effect of Tyramin on Blood Pressure, Pulse Rate and Volume Pulse

Case	Hospital Number		Dose Gm	Blood Pressure			Pulse Rate	Volume Pulse	Sustained Quality
				Systolic	Diastolic	Pulse			
1	59747	Before		118	85	33	64	0 39	
		After	0 06	200	92	108	44	0 68	Increased
2	59947	Before		125	79	46	68	0 65	
		After	0 065	203	95	108	54	0 70	No change
3	60120	Before		100	57	43	100	0 90	
		After	0 06	160	70	90	72	1 2	Increased
4	57928	Before		106				0 55	
		After	0 06	160				1 0	Increased
5	58322	Before		120	50	70		1 20	
		After	0 08	170	52	118		1 48	No change
6	57783	Before		120	72	48		0 55	
		After	0 04	170	83	87		0 69	Increased
7	57676	Before		131	80	51		0 85	
		After	0 05	180	84	96		1 25	No change
8	59876	Before		120	82	38	57	0 47	
		After	0 06	165	90	75	45	0 60	No change
9	58051	Before		115	85	30		0 88	
		After	0 05	155	90	65		1 05	Increased
10	59732	Before		100	70	30	55	1 10	
		After	0 06	134	80	54	48	0 90	No change
11	59732	Before		113	86	27	56	0 92	
		After	0 06	134	90	44	52	0 95	No change
12	59856	Before		155	85	70	107	0 72	
		After	0 05	180	85	95	94	0 87	No change

EFFECT ON THE VOLUME PULSE IN THE ARM

In twelve experiments the volume pulse of the forearm and lower arm was recorded by using a plethysmograph which was connected with a Frank capsule by air transmission Calibration was made in

each experiment by introducing into or withdrawing from the plethysmograph 2 c c of air while the arm was in place The average change on the records produced by several such tests was taken to indicate the effect resulting from a 2 c c change in arm volume

Table 1 shows that in nine of the twelve experiments a distinct increase (over 0 1 c c) in the size of the volume pulse in the arm

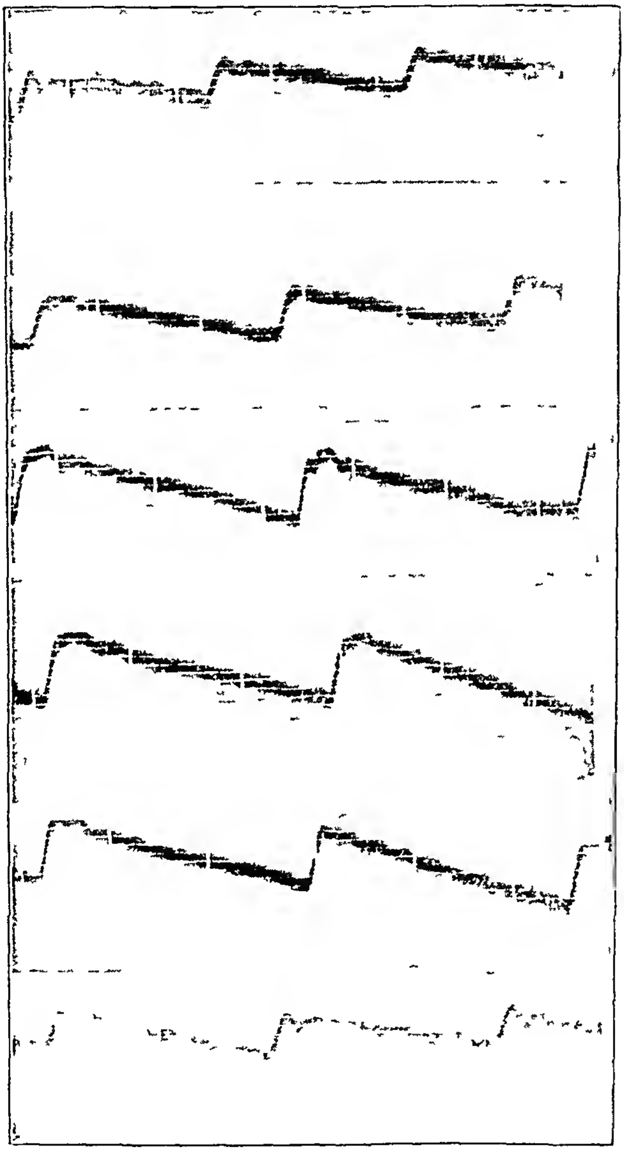

Fig 2—The volume pulse in the arm after tyramin (Case 1 of Table 1 and Figure 1) First record taken before, second 4 minutes after, third 8 minutes after, fourth 15 minutes after, fifth 18 minutes after and last 30 minutes after the injection of 0 06 gm tyramin The changes in the size and form of the pulse waves were most marked in the third and fourth records

occurred at the height of the tyramin action, in two instances the recorded increase was so slight as to be doubtful, while in one instance the volume pulse was distinctly lessened This increase in the volume

of the arm pulse was, as we shall see, pıesumably due to a larger output of blood at each cardıac systole

The form of the volume pulse was altered ın five of the twelve experıments, and ın each case thıs alteıatıon was ın the dıiectıon of a more sustaıned pulse In Fıgure 2, for example, the pıımary pulse wave was followed by an anacrotıc plateau at the heıght of the tyramın effect In Fıgure 3 from a patıent wıth typhoıd fever, the collapsıng qualıty of the febrıle pulse became less marked Such changes were not constant, however, and ın many ınstances no defınıte alteıatıon ın the form of the arm pulse was noted durıng the heıghtened systolıc pressure and slow pulse produced by the tyramın ınjectıon

In four ınstances satısfactory records of the blood flow ın the arm were obtaıned These showed no marked and constant alteratıon In

TABLE 2—Effect of Tyramin on the Electrocardiogram

Case	Hospital Number		Dose, Gm	Systolic Pressure	Pulse Rate	Lead I			Lead II			Lead III		
						P	R	T	P	R	T	P	R	T
13	56167	Before		110	75	1 0	6 0	1 0	1 2	18 0	0 5	0 5	15	0 0
		After	0 06	162	82	0 0	6 5	4 0	1 5	20 0	5 0	1 8	17	1 5
14	57676	Before		113	85	0 2	3 0	1 7	2 5	9 0	2 0	2 2	7	0 5
		After	0 05	140	80	0 2	3 0	2 0	2 5	9 0	5 2	2 5	6	2 5
15	58845	Before		135	90*	0 8	5 5	1 7	2 0	12 0	1 3	1 0	7	0 0
		After	0 06	160	106*	0 3	4 5	2 7	2 8	11 0	2 5	2 0	7	0 5
16	57928	Before		102	84	1 0	9 5	3 0	0 7	16 0	2 5	0 5	8	
		After	0 06	130	73	0 7	8 0	5 0	0 7	15 0	4 8	0 3	9	
17		Before		135	63	No change								
		After	0 06	122	60									

* Sinus rate Numerous ventricular extrasystoles occurred (Fig 6)

one case no change occurred, ın a second there was a slıght ıncrease durıng the heıghtened blood pressure, wıth a slıght dımınutıon when the pressure fell, whıle ın the remaınıng two there was a gradual ıncrease ın the rate of flow, whıch contınued after the pressure fell Whatever may have been the cause of thıs gradual ıncrease, ıt was not defınıtely related to the varıatıons ın the blood pressure

EFFECT OF TYRAMIN ON THE ELECTROCARDIOGRAM

In five patıents electrocardıograms were taken before the admınıstratıon of tyramın and agaın at the heıght of the rıse of blood pressure The ınstrument was carefuly adjusted before each record wıth the patıent ın cırcuıt so that a deflectıon of 10 mm should correspond to a current of 1 mıllıampere Of these five patıents, one showed no rıse of blood pressure after the ınjectıon and no change ın the electrocardıogram In the remaınıng four patıents the change ın blood

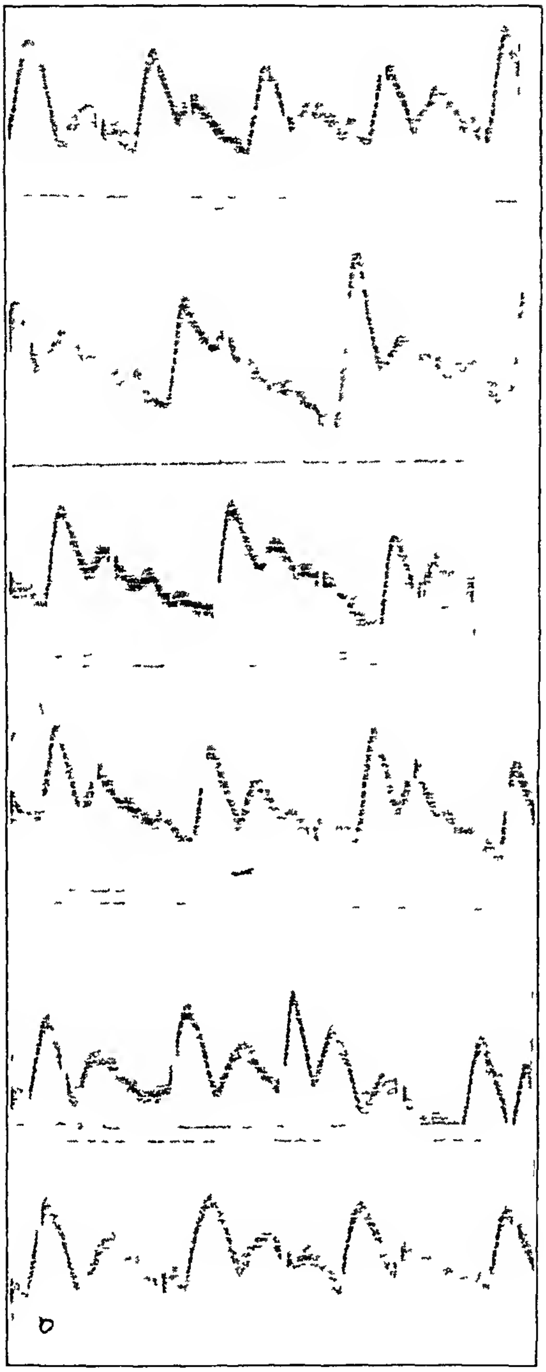

Fig 3—The volumes pulse in the arm after tyramin (Case 3 of Table 1 and Figure 1), a patient with typhoid fever First record before, second 4 minutes after third 7 minutes after, fourth 8 minutes after, fifth 11 minutes after and last 13 minutes after the injection of 0 06 gm tyramin The change in size and form of the pulse was most marked in the second and third records In this patient the maximum effect occurred unusually early A premature beat is seen in next to the last record

pressure was accompanied by definite alterations in the form of the electrocardiogram These may be seen by referring to Table 2 and to Figures 4, 5 and 6 The most constant of these changes was an increase in the size of T This occurred in every instance in which T was originally upright In one patient where T was originally small and diphasic in Lead III (Figure 5), it became somewhat more definite after tyramin, but the diphasic character of the wave did not permit of expressing the change numerically In another patient, not included in Table 2 because the instrument had not been carefully calibrated before each record, T was negative in Lead III before the injection and it apparently became more so under the influence of tyramin

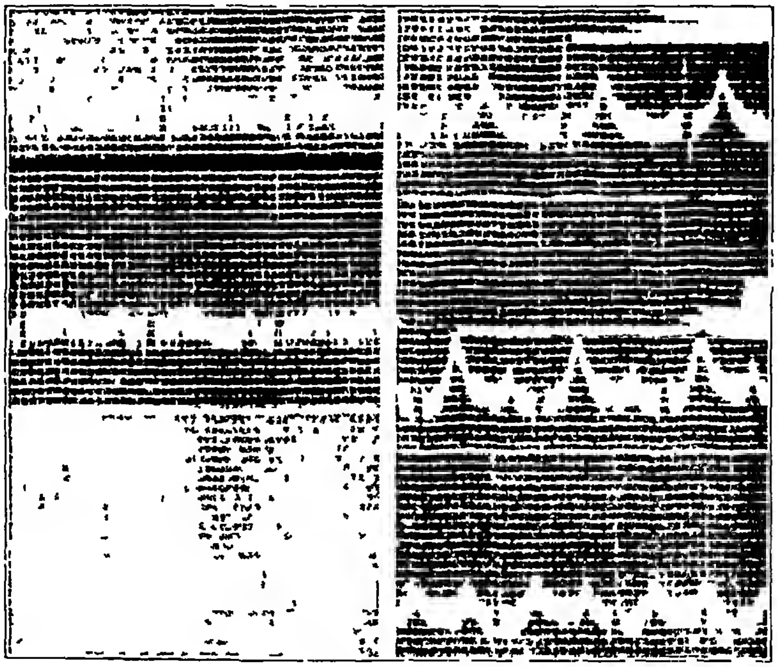

Fig 4—Electrocardiograms taken before (left) and after (right) the injection of 0 06 gm tyramin (Case 13, Table 2) T became larger in all leads, P became smaller in Lead I and larger in Lead III

Changes in the other waves of the electrocardiogram, though present in certain instances, were not constant The QRS complex was on the average unaffected P showed a slight but not invariable tendency to be diminished in Lead I and increased in Lead III

Augmentation of T has been described by Rothberger and Winterberg[9] after accelerator stimulation, and by Lewis and Cotton[10] and others following exercise In these conditions, however, P also

9 Rothberger, J, and Winterberg, H Ueber die Beziehungen der Herznerven zur Form des Elektrokardiogramms, Arch f d ges Physiol, 1910, **135,** 506

10 Lewis, T, and Cotton, T F The "P-R" Interval in Human Electrocardiograms and Its Relation to Exercise, Proc Physiol Soc, June 28, 1913, Jour Physiol, 1913, **46,** 60

increased in size, whereas this did not occur after tyramin injections, except in Lead III

THE PRODUCTION OF EXTRASYSTOLES

On four or five occasions it was noted that extrasystoles, previously absent, occurred during the action of tyramin Such a premature beat is seen in next to the last tracing of Figure 3 Before this fact was fully appreciated, a patient already showing occasional ventricular extrasystoles was given an injection of tyramin in order to determine if this might influence the irregularity in a favorable manner In place

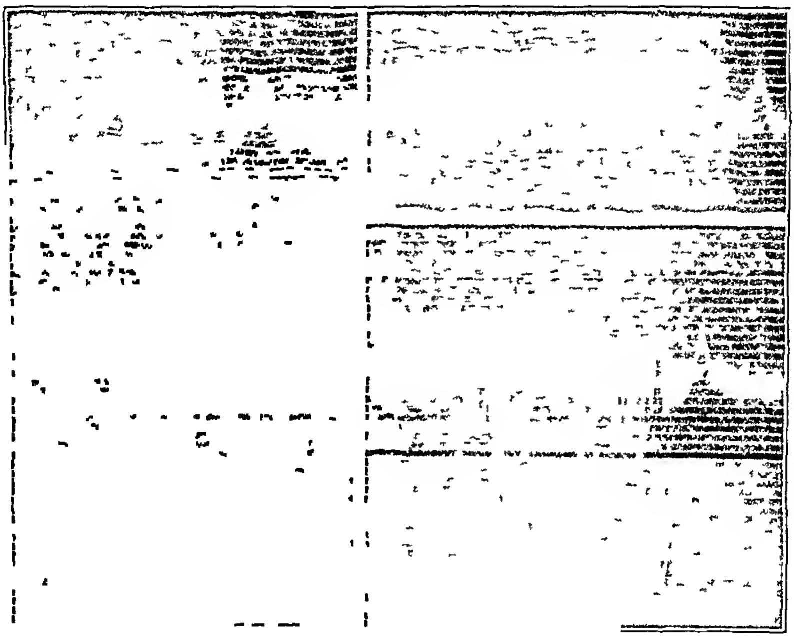

Fig 5—Electrocardiograms taken before (left) and after (right) the injection of 0 06 gm tyramin (Case 16, Table 2)

of a favorable effect, there was an increase in the number and variety of abnormal ventricular contractions (Fig 6)

Levy produced ventricular fibrillation in a cat under chloroform anesthesia by injecting tyramin[11] Inasmuch as there is a close relationship between ventricular fibrillation and very numerous ventricular extrasystoles, it seems possible that under proper conditions tyramin might cause a dangerous or even fatal ventricular fibrillation in man Caution is therefore urged in the use of this drug if ventricular extrasystoles are already present or if there is reason to suspect a condition

11 Levy, A G The Genesis of Ventricular Extrasystoles Under Chloroform, with Special Reference to Consecutive Ventricular Fibrillation, Heart, 1913-1914, 4, 299

of increased irritability in the heart muscle such as seems to occur during chloroform anesthesia

EFFECTS PRODUCED BY SUBCUTANEOUS INJECTIONS OF EPINEPHRIN

In susceptible individuals, subcutaneous injections of epinephrin frequently produce symptoms and signs which resemble those of exophthalmic goiter Within a few minutes the individual experiences

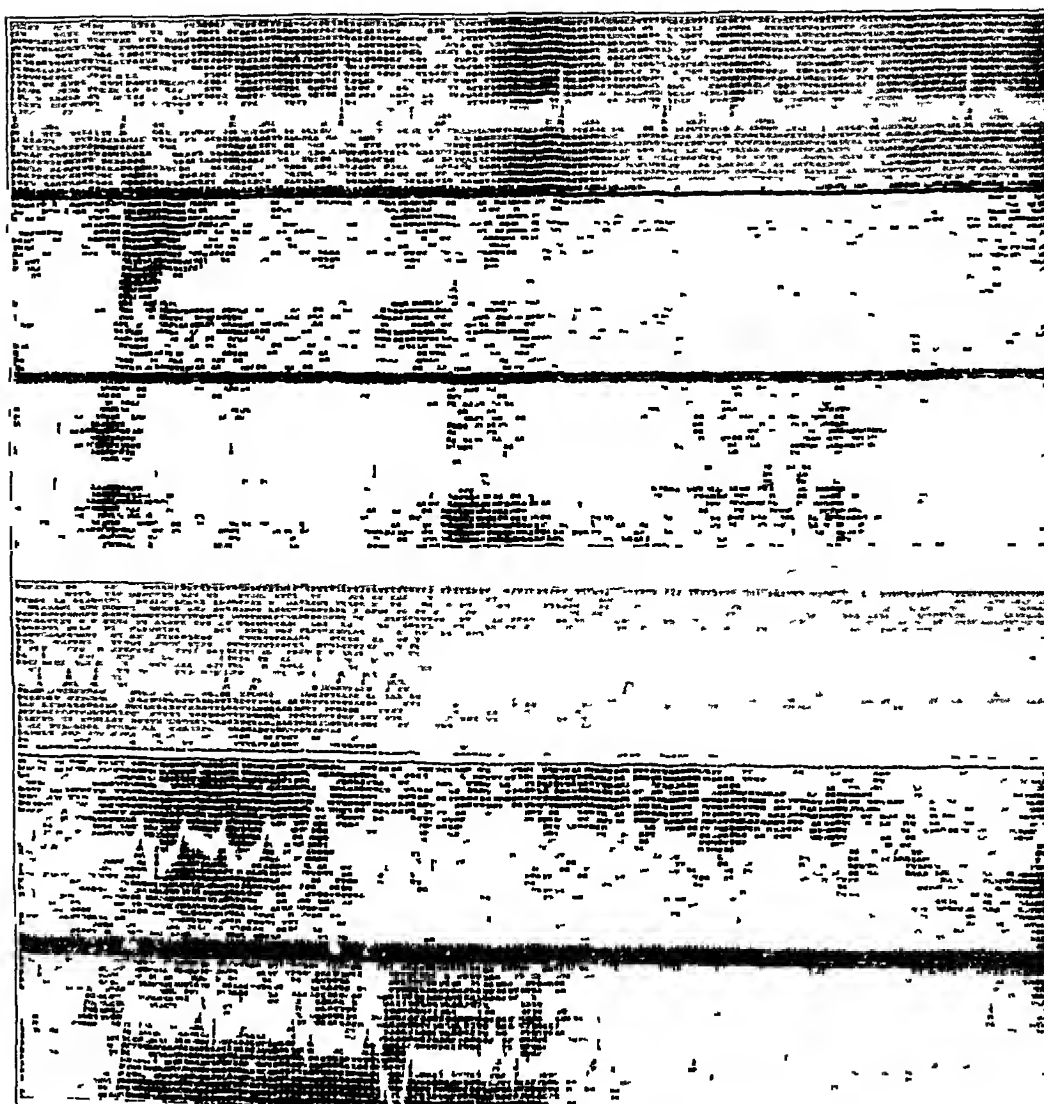

Fig 6—Increased number of extrasystoles caused by tyramin Record above taken before and record below taken after the injection of 0 06 gm (Case 15, Table 2)

tremulous sensations which are demonstrable objectively as a tremor of the extended hands This tremor seems to be somewhat coarser and less regular than is the typical tremor of exophthalmic goiter, and it frequently involves the arms as well as the hands and fingers In

addition the susceptible person often feels anxious and nervous, and is conscious of palpitation and uneasy sensations about the precordium and epigastrium Patients with exophthalmic goiter are particularly prone to exhibit distressing symptoms of this type after epinephrin injections, and several have said to the author that for the time being the usual symptoms of their disease became much worse For this reason a considerable number of epinephrin injections were given to nervous persons with the hope that the degree of reaction might prove of some value in the diagnosis of incipient exophthalmic goiter No

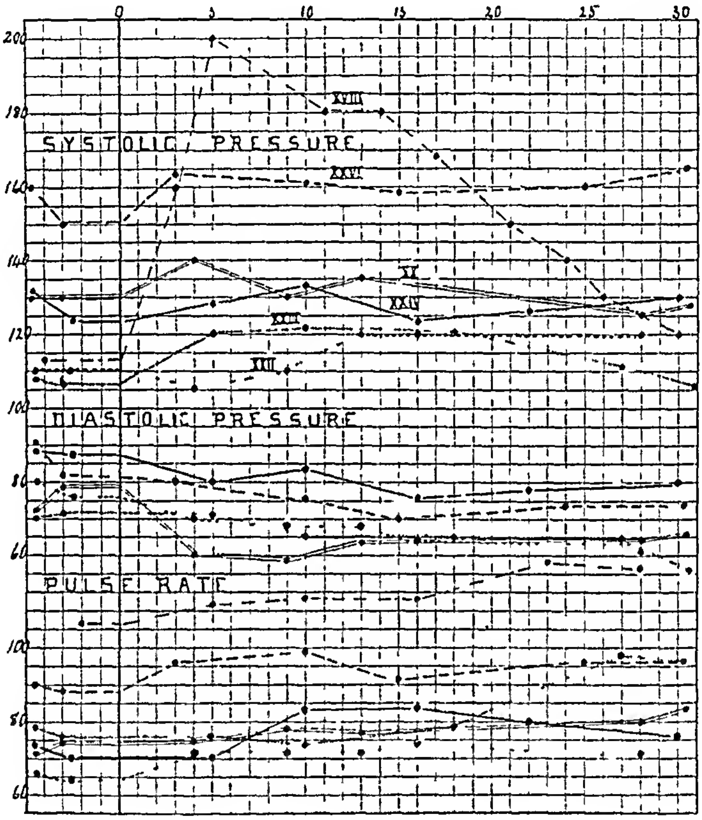

Fig 7—Chart showing the effect of subcutaneous injections of epinephrin on the systolic and diastolic blood pressure and on the pulse rate The Roman numerals correspond to the cases in Table 3 The marked rise of blood pressure (Case 18) was in a patient with exophthalmic goiter In this patient auricular extrasystoles also occurred, most numerous at sixteen minutes and less numerous at twenty-three and twenty-eight minutes after the injection

definite relation was found, however, between susceptibility to epinephrin and the milder degrees of hyperthyroidism as judged clinically In making these tests a number of records were made of the circulatory changes produced by subcutaneous injections of epinephrin These will be reviewed briefly in order to contrast them with the circulatory changes induced by tyramin

It is well known that the marked rise of blood pressure which occurs after the intravenous injection of a large dose of epinephrin is rarely observed when the drug is administered subcutaneously The gradual absorption from the subcutaneous tissues, together with its destruction or disappearance in the tissues, prevents any marked rise in the concentration of epinephrin in the blood Even though there is little or no rise in the blood pressure, nevertheless subcutaneous injections of epinephrin often produce definite physiologic effects in man In addition to the tremor, nervousness and palpitation, we may mention the occasional production of glycosuria and the remarkable relief from asthmatic paroxysms that is often afforded by this drug It is now known that in laboratory animals intravenous injections of small doses of epinephrin usually cause a fall of blood pressure and a dilatation of certain vascular areas, particularly those supplying the muscles in the extremities [12] Analogous effects might be anticipated, when, owing to its subcutaneous administration to man, the absorption is slow

Like others, we found that the changes in blood pressure after subcutaneous injections of epinephrin into patients varied considerably (Fig 7 and Table 3) Occasionally there was a very marked rise in the systolic blood pressure similar to that produced by intravenous injections of the drug, but as a rule the systolic pressure rose only moderately or at times not at all The diastolic pressure rarely rose

In most cases it was either uninfluenced to any definite degree or it showed a distinct fall Watson,[13] who was much impressed with this fall, suggested that inasmuch as "adrenalin had been proved so clearly to cause contraction of the peripheral vessels" the fall of diastolic pressure was attributable to a temporary aortic regurgitation In the light of our present knowledge of the vasodilator action of epinephrin, however, it appears more reasonable to attribute the fall of diastolic pressure to vascular relaxation

In our experience the most constant effect of this drug on the blood pressure was an increase in the difference between the systolic and diastolic pressures, that is, in the pulse pressure There was also in almost every instance a very definite increase in the loudness of the

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12 Cannon, W B, and Lyman, H The Depressor Effect of Adrenalin on Arterial Pressure, Am Jour Physiol, 1913, **31**, 376 Hartman, F A The Differential Effect of Adrenalin on Splanchnic and Peripheral Arteries, Am Jour Physiol, 1915, **41**, 513 Hoskins, R G, Gunning, R E L, and Berry, E L The Effect of Adrenin on the Distribution of the Blood, Am Jour Physiol, 1916, **42**, 513, 1917, **43**, 399 Hartman, F A, and McPhedran, L Further Observations on the Differential Action of Adrenalin, Am Jour Physiol, 1917, **43**, 311

13 Watson, A Some Observations on the Effect of Hypodermic Injections of Adrenalin on the Blood Pressure, Practitioner, London, 1914, **92**, 94

vascular sounds which are heard below the pressure cuff during the auscultatory determinations of blood pressure

The pulse rate after subcutaneous injections of epinephrin was usually somewhat increased (Fig 7, Table 3) The volume pulse in the arm became larger (Table 3), and its form, while often unaltered, tended to become more collapsing (Table 3, Fig 8) This change suggested a vascular relaxation in the arm Unfortunately, no records

TABLE 3—Effect of Subcutaneous Injection of Epinephrin

Case	Hospital Number		Dose, 1 1,000 Solution, Minims	Tremor	Blood Pressure Systolic	Blood Pressure Diastolic	Blood Pressure Pulse	Pulse Rate	Volume Pulse	Sustained Quality
18	56167	Before After	 15	+ +++	113 200			112 124		
19	54169	Before After	 7	0 +++	125 155	 80	 75	84 104	0 32 0 86	Lessened
20	54276	Before After	 10	0 +	130 135	75 64	55 71	72 84	1 2 1 85	Lessened
21	53938	Before After	 10						0 9 1 5	Lessened
22	54718	Before After	 8	0 +	110 120	78 64	32 56	65 74	0 75 1 3	Lessened
23	54241	Before After	 10	+ +++	106 {122 {105	71 65 50	35 57 55	76 74} 96}	0 85 1 2	No change
24	54035	Before After	 10	0 +	128 {134 {124	88 84 76	40 50} 48}	72 84	0 6 0 9	Lessened
25	54263	Before After	 10	+ ++	109 {108 {104	68 70 64	41 38} 40}	64 70	0 7 1 0	No change
26	54280	Before After	 10	+ ++	155 {164 {158	86 84 79	69 80} 88}	89 96	0 8 1 0	Lessened
27	54745	Before After	 6	+ ++	119 122	81 74	38 48	66 76	0 6 0 7	No change
28	17526	Before After	 7	+ +	128 122	88 84	40 38	82 82	1 1 1 2	No change

were made of the rate of blood flow through the arm before and after epinephrin injections

A few electrocardiograms were taken before and after the injections In some there was a distinct increase in T similar to that produced by tyramin, in others this change was slight or did not occur This increase of T was most marked in a patient who also showed a striking rise of systolic pressure (Case 18), but its relation to the blood pressure changes was not further studied

The circulatory alterations produced by tyramin, by epinephrin, by pituitary extract and by nitroglycerin are compared in Table 4 From this it will be seen[1] that tyramin resembles pituitary extract in that

both tend to raise the diastolic pressure and to cause a more sustained pulse, (2) that epinephrin resembles nitroglycerin in that both tend to lower the diastolic pressure and to cause a more collapsing pulse, while (3) tyramin and epinephrin resemble each other in that both cause a definite increase of pulse pressure, augmentation of T in the electrocardiogram and occasional extrasystoles

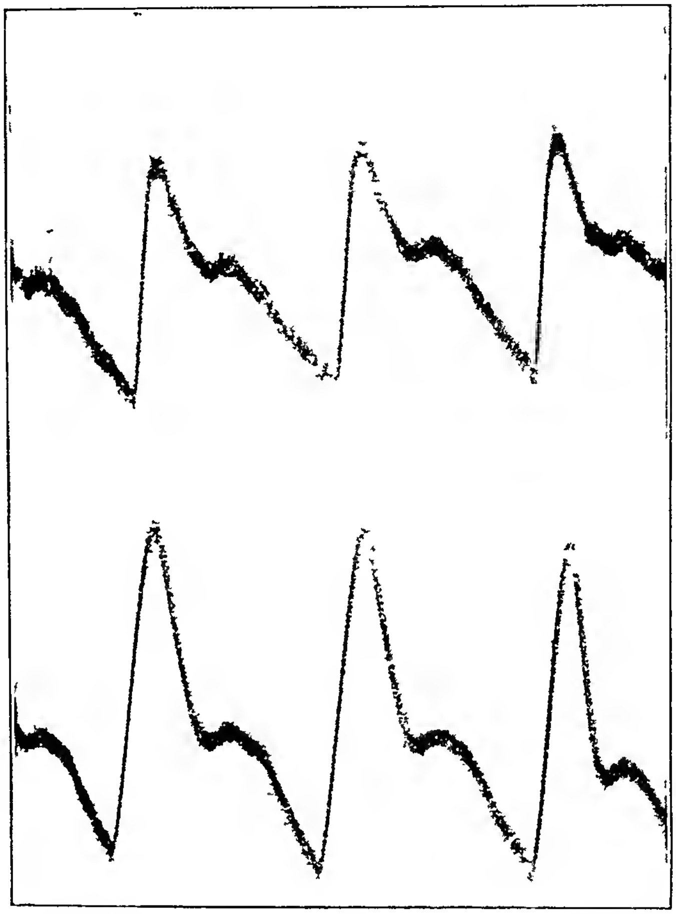

Fig 8—Volume pulse in the arm after the subcutaneous injection of 10 minims epinephrin solution (1 to 1,000) Upper before and lower twenty-four minutes after the injection (Case 20 of Fig 7 and Table 3)

DISCUSSION

The most striking circulatory changes that we have observed in man after injections of tyramin may be summarized as follows

(*a*) an increase in the systolic blood pressure, the pulse pressure and the volume pulse in the arm,

(*b*) a slowing of the heart rate, and

(*c*) an increase in the size of T in the electrocardiogram with the occasional occurrence of extrasystoles

The increase in pulse pressure appears to be due mainly to an increased output of blood with each ventricular systole It is true that an increased pulse pressure might conceivably result from a constriction or a heightened tone of the blood vessels In such a case,

however, one would expect to find a far greater rise in the diastolic pressure than was actually observed Furthermore, we know that certain drugs which act primarily on the blood vessels produce characteristic changes in the volume pulse of the arm Nitroglycerin, a typical vasodilator, causes the arm pulse to become larger and more collapsing,[15] whereas pituitary extract, a typical vasoconstrictor, causes the collapsing pulse of febrile patients to become smaller and more

TABLE 4—Comparison of the Usual Effects on Man of Pituitary Extract, Tyramin, Epinephrin and Nitroglycerin

	Pituitary Extract	Tyramin	Epinephrin	Nitroglycerin
Mode of administration	Intramuscularly	Subcutaneously	Subcutaneously	On tongue
Systolic pressure	No constant change[14]	Marked increase	Usual increase, varies from little change to marked increase	Diminished
Diastolic pressure	Increased[14] (febrile pulse)	Slight increase or no change	Diminished or no change	Diminished
Pulse pressure	Diminished[14] (febrile pulse)	Marked increase	Moderate increase	
Pulse rate	Occasional slight slowing[14]	Marked slowing	Some increase	Some increase[15]
Volume pulse in arm	Diminished[16] (febrile pulse)	Increased	Increased	Increased[15]
Sustained quality of arm pulse	More sustained[16] (febrile pulse)	More sustained or no change	Less sustained or no change	Less sustained[16]
T wave in electrocardiogram	No change	Augmented	No change or augmented	No change [1]
Tendency to produce ventricular extrasystoles	Apparently none	Present	Present[16]	None

sustained[16] After tyramin the arm pulse becomes larger, but its form, if altered at all, is more sustained Such a change is not typical of vascular constriction, and is more readily explained on the assumption that there is an increased systolic output from the heart

Inasmuch as this increased output at each cardiac contraction is accompanied by a reduction in the heart rate, the question arises whether the total cardiac output in a unit of time is affected by tyramin Our data do not furnish an accurate measure of the cardiac output If this is roughly proportional to the product of heart rate × pulse pressure, then it would appear that tyramin materially increases the total cardiac output, for under its influence the above product is often

14 Schmidt, H B The Effect of Pituitary Injections on the Blood Pressure of Febrile Patients, The Archives Int Med, 1917 **19,** 1059

15 Hewlett, A W Van Zwaluwenburg, J G and Agnew, J H The Pulse Flow in the Brachial Artery The Archives Int Med, 1913 **12,** 7

16 Hewlett A W The Pulse Flow in the Brachial Artery the Influence of Certain Drugs, The Archives Int Med, 1917, **20,** 1

increased by 50 to 100 per cent One must recognize, however, that various fallacies are possible in reasoning from these data It is not our intention therefore to insist that tyramin, which has been demonstrated in animal experiments to possess a vasoconstrictor action, is without such an action when injected into man We wish rather to point out that by the methods used an increased cardiac output seems probable, whereas vascular effects that were comparable to those produced by pituitary extract could not be demonstrated

Subcutaneous injections of epinephrin also caused an increase in pulse pressure which was accompanied by a slight to moderate increase in the pulse rate The product, heart rate × pulse pressure was therefore increased, and this may again be taken, with some reserve, to indicate that the cardiac output was increased by subcutaneous injections of this drug As compared with tyramin, however, the action of epinephrin, injected subcutaneously, was characterized by evidence of vascular relaxation In the first place, the diastolic blood pressure usually fell In the second place, the arm pulse usually became larger and it often became more collapsing, changes that are comparable to those produced by the administration of nitroglycerin This view that subcutaneous injections of epinephrin usually relax the blood vessels, particularly in the arm, is in accord with recent animal experiments which have demonstrated that small doses of epinephrin may reduce the blood pressure and that the drug in appropriate doses dilates various vascular areas, particularly those supplying the voluntary muscles and the intestines [12]

Tyramin not only alters the heart rate and the systolic output, but it modifies the ventricular contractions in other ways, as is shown by the augmentation of T in the electrocardiogram and by the occasional production of ventricular extrasystoles The cause of these changes has not been determined Among their possible causes are mechanical alterations in the circulation owing to the increased systolic output and the heightened blood pressure, nervous influences such as accelerator stimulation in addition to the vagus inhibition, and finally, a direct effect of the drug on the ventricular muscle We have pointed out that similar changes in the electrocardiogram as well as occasional ventricular extrasystoles have been induced by epinephrin According to Levy[11] the ventricular irregularities produced in animals by epinephrin cannot be explained solely by the alterations of blood pressure and Roth[17] found no relation between the pressure changes and the ventricular extrasystoles induced in cardiac patients by epinephrin injections By analogy, therefore, it would seem probable that the extrasystoles induced by tyramin are due in part to other causes than the changes in blood pressure and cardiac output

17 Roth, O Ueber die Reaktion des Menschlichen Herzens auf Adrenalin, Deutsch med Wchnschr 1914, 40, 905

OBSERVATIONS REGARDING THE LOSS OF WATER VAPOR THROUGH THE SKIN IN INFANTS*

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The elimination of heat from the body is dependent almost entirely on radiation, conduction and evaporation While it is possible to determine the sum total of heat loss of an individual, the accurate determination of the parts entering into this sum is beset with difficulties which have not as yet been surmounted Nevertheless, even relatively simple methods can yield some information, if not of the amount of heat lost by one or the other mechanism, at least about some of the conditions exercising an influence thereon Thus, a study of the surface temperature gave us some data[1]— more accurate than available before — concerning the heat loss by conduction and radiation In this communication we wish to report data with regard to the evaporation of water from the body surface other than the loss of water through lungs and sweat, that is, the so-called *insensible perspiration*

The observations of Loewy,[2] made on individuals whose skin was devoid of sweat glands, would seem to demonstrate that insensible perspiration is entirely independent of the sweat glands

Attempts to determine the amount of water eliminated from the skin in the form of insensible perspiration have been made by a considerable number of workers using various direct and indirect methods The literature on the subject is excellently reviewed in the paper of Soderstrom and DuBois[3] None of the direct methods seems to have been applied to the infant In our review of the literature we were not able to find any work in which the loss of water through the skin was determined separately from that through the lungs In infancy insensible perspiration would seem to be of special importance because the sweat glands usually do not functionate during this period of life The determination of the insensible perspiration from the total skin surface would be most desirable Such a procedure, if at all feasible,

* Submitted for publication Jan 22, 1918

* From the Otho S A Sprague Memorial Institute Laboratory of the Children's Memorial Hospital

1 McClure and Sauer Am Jour Dis Child, 1915, **10,** 425

2 Loewy Biochem Ztschr, 1914, **67,** 243

3 Soderstrom and Du Bois The Archives Int Med, 1917, **19,** No 5, Part II, p 931

would be very difficult indeed Some data with regard to the loss of water from a restricted area of the skin were obtained, however, by a simple method kindly suggested to us by Prof H G Gale of the Department of Physics of the University of Chicago A current of room air was drawn over an area of skin and subsequently through a set of calcium chlorid tubes properly prepared The air current was maintained by means of a water syphoning apparatus, the rate of flow was regulated readily by measuring the water withdrawn from the syphoning bottle during a unit of time A rectangular metal box of 4 5 cm depth and 7 5 by 5 cm top was placed on the skin with the open bottom enclosing an area of 37 5 square centimeters This box was placed on the chest, and a control box of exactly the same dimensions, but closed on all sides, was placed immediately next to it The tubes for the entrance and exit of the air were at opposite ends of the boxes and at different levels, thus insuring better ventilation The control box was also connected with calcium chlorid tubes and syphon By this arrangement the conditions for control and experiment were as nearly alike as possible Temperature and humidity of the room air were also determined The calcium chlorid tubes of the two systems were weighed before and after each observation, the control giving the water absorbed from the air, the other, the water from the air, and in addition that given off by the skin In this way the amount of water given off by 37 5 square centimeters of skin was determined A number of blank experiments were made to test the accuracy of our method The difference between the two sets of tubes in the blank experiments never was as great as 1 mg

We preferred the method described to the one employed by Galeotti and Macri [4] Their apparatus consists of a small metal box with a sliding lid and with calcium chlorid fragments fastened to the inner surface The box is weighed and placed on the skin and the lid withdrawn After fifteen minutes the lid is replaced and the box again weighed The gain in weight determines the insensible perspiration This method is open to the objection that the apparatus is really a desiccator and, in addition, all of the carbon dioxid given off by the skin is included in the determination

In selecting the part of the skin to be studied the chest was decided on because of the convenience of applying the metal box over this rather large and relatively flat surface, this portion of the body is also relatively immobile in the infant, in whom the abdominal type of respiration prevails The arrangement of our experiments gives figures for only a limited area of skin Galeotti and Macri[4] and Loewy[2] have shown that different areas of skin give off different

4 Galeotti and Macri Biochem Ztschr, 1914, **67**, 472

amounts of water vapor We cannot, therefore, with our method obtain any accurate data with reference to the total loss of water by insensible perspiration through the skin, but we can obtain information about the variations of a given area and about some factors influencing the insensible perspiration in this area

RATE OF VENTILATION

In choosing the rate of air flow it was desired to maintain a sufficient ventilation to prevent an accumulation of moisture in the metal box overlying the skin and yet avoid a cooling effect For our first determinations we used an air flow of 7 liters per hour In this way the air in the box was renewed 41 5 times per hour Later some experiments were made to see what effect a more rapid rate of ventilation would have These determinations were made on an adult, as it is of importance that the subject be quiet during the observations The subject was seated and wore ordinary indoor clothing The chest

TABLE 1—INFLUENCE OF VARIOUS RATES OF VENTILATION

No	Room Temp, C	Rate	No of Renewals per Hr	Gm H_2O per 37 5 Sq Cm	Gm H_2O* per Sq dm per Hr
1	19	7 L per 60 min 14 L per 60 min	41 5 83 0	0 0137 0 0204	0 0365 0 0544
2	20	7 L per 60 min 14 L per 60 min	41 5 83 0	0 0124 0 0354	0 0331 0 0944
3		7 L per 60 min 14 L per 60 min	41 5 83 0	0 0164 0 0247	0 0437 0 0659
4	18	7 L per 60 min 14 L per 60 min	41 5 83 0	0 0083 0 0112	0 0221 0 0299
5	21	7 L per 43 min 14 L per 43 min	58 0 116 0	0 0014 0 0032	0 0052 0 0130
6	23	7 L per 43 min 14 L per 43 min	58 0 116 0	0 0047 0 0169	0 0175 0 0629
7	18 5	14 L per 60 min 21 L per 60 min	83 0 124 5	0 0252 0 0189	0 0672 0 0504
8	19 5	14 L per 53 min 28 L per 53 min	93 9 187 8	0 0356 0 0320	0 1075 0 0966
9	20	14 L per 43 min 21 L per 43 min	116 0 173 6	0 0035 0 0064	0 0130 0 0238
10	20	14 L per 43 min 21 L per 43 min	116 0 173 6	0 0062 0 0085	0 0231 0 0343
11	20	21 L per 60 min 28 L per 60 min	124 5 166 0	0 0472 0 0285	0 1260 0 0760
12	20	21 L per 43 min 28 L per 43 min	173 6 231 5	0 0097 0 0095	0 0360 0 0353
13	20	21 L per 43 min 28 L per 43 min	173 6 231 5	0 0106 0 0097	0 0394 0 0360

* The value in grams of water per square decimeter per hour in all of our tables are given for convenience of comparison with the figures of other observers

was uncovered sufficiently to place the boxes on the skin Each experiment consisted of two determinations following one another with just enough time intervening for weighing the calcium chlorid tubes Deductions can, of course, be made only from such successive determinations, as it has been shown by Loewy[2] that the amount of insensible perspiration may vary considerably in the same individual on successive days under approximately similar conditions of temperature and humidity, a fact also very well illustrated in our observations

It is seen that an increase in the rate of ventilation up to a certain point is accompanied by an increase of the values for insensible perspiration When the rate is increased beyond this, there is not only no further increase, but even a decrease A vasoconstriction in consequence of cooling suggests itself as a plausible explanation for this decrease It may be mentioned that Loewy[2] has shown a definite decrease of the insensible perspiration on cooling the skin surface

INSENSIBLE PERSPIRATION OF THE NORMAL INFANT

Table 2 gives the results of determinations of insensible perspiration in convalescent and normal infants In Nos 1 to 3 the infants wore only cotton diapers and the rate of ventilation was 7 liters per hour In Nos 4 to 8 the babies wore cotton stockings, cotton undershirts and diapers The undershirts were opened over the chest to allow the apparatus to come in contact with the skin The rate of ventilation was 14 liters per forty minutes Of the latter group, in Nos 6c and 6d the child was restless In 6e the child was fretful and cried at times Nos 7 and 8 give the results obtained from observations on the same infants serving for Nos 2 and 3, but with the room temperatures from 5 5 to 7 degrees C higher The relative humidity was about the same in all observations, that is, around 30 per cent With restlessness, with fretfulness and crying, and with increased room temperature relatively high figures were obtained for the insensible perspiration One must be guarded in concluding that these factors actually determine an increase of insensible perspiration because of the variations which occur from day to day without any attributable cause, and the observations in the table were made on different dates We have a number of other observations, however, which give additional evidence in support of such an effect It happened rather frequently that an infant became fretful or cried in the course of experiments intended to test the effect of various factors on the insensible perspiration, such as the effect of clothing, etc Such determinations, of course, had to be discarded, but invariably relatively high figures were obtained In other words, whenever we had to deal with a restless, fretful or crying baby or whenever we had occasion to repeat an observation on any infant at a room temperature

decidedly higher than previously, the insensible perspiration was invariably greater The sum total of our observations indicates strongly that the factors just discussed actually lead to an increase of the insensible perspiration

TABLE 2—Bare Chest

A Average Room Temperature

No	Age, Mos	Wt, Kg	Rect Temp, C	Room Temp, C	Rate of Ventilation	Gm H_2O per 37 5 Sq Cm	Gm H_2O per Sq dm per Hr	Diagnosis	Remarks
1	4½	4	37	23 5	7 L per 60 min	0 0288	0 0768	Convalescent from gastro enteritis	Quiet
2	4	4	37	23	7 L per 60 min	0 0262	0 0698	Convalescent from gastro enteritis	Quiet
3a*	9	5	37	23	7 L per 60 min	0 0198	0 0510	Convalescent from atro phy	Quiet
3b	9	5	36 5	23	7 L per 60 min	0 0190	0 0506	Convalescent from atro phy	Quiet
4	7	6	36	21	14 L per 40 min	0 0252	0 1512	Convalescent from gastro enteritis	Quiet
5	4	6	37	25	14 L per 40 min	0 0725	0 4350	Normal	Quiet
6a	10	8	37	24	14 L per 40 min	0 0390	0 2340	Normal	Quiet
6b	10	8	37 5	26	14 L per 40 min	0 0504	0 3024	Normal	Quiet
6c	10	8	37	25	14 L per 40 min	0 0637	0 3822	Normal	Somewhat restless
6d	10	8	37 5	24 5	14 L per 40 min	0 0681	0 4086	Normal	Somewhat restless
6e	10	8	37 5	26	14 L per 40 min	0 1325	0 7950	Normal	Very rest less crying at times
B High Room Temperature									
7a	4	4	37	28 5	7 L per 60 min	0 0546	0 1430	Convalescent from gastro enterit s	Quiet
7b	4	4	37	30	7 L per 60 min	0 0634	0 1610	Convalescent from gastro enteritis	Quiet
8	9	5	37	29	7 L per 60 min	0 0356	0 0949	Convalescent from atro-phy	Quiet

* In tables, letters following numerals indicate additional observations on the same individuals

INFLUENCE OF CLOTHING

In attempting to determine what effect clothing has on the amount of water vapor given off to the surrounding air, we made determinations with the metal box placed on the clothing overlying the chest and followed these almost immediately with determinations on the

bare chest The results obtained in these observations were quite variable

In one adult, for instance, the amount of moisture given off through the clothing (which consisted of two layers of cotton clothing that had been worn for seven to eight hours) corresponded closely with the amount given off from the bare skin of the same region (Table 3A)

In another adult with similar clothing, which had been worn for eight hours, there were somewhat greater variations (Table 3B)

In a series of observations on infants where the clothing consisted of two layers of cotton material (the ordinary cotton hospital clothing

TABLE 3—Showing the Influence of Clothing

Adults

	No	Surface	Hours Clothing on	Rate	Values	Subject and Date	Kind of Clothing
A	1	Over cloth	8	14 L 1 hr	0 0235	McC 4/11/17	Two layers of cotton clothing
		Bare		14 L 1 hr	0 0246		
	2	Over cloth	7	14 L 1 hr	0 0185	McC 4/12/17	Two layers of cotton clothing
		Bare		14 L 1 hr	0 0175		
	3	Over cloth	7	14 L 1 hr	0 0234	McC 4/13/17	Two layers of cotton clothing
		Bare		14 L 1 hr	0 0231		
B	4	Over cloth	8	14 L 40 min	0 0127	S 9/28/17	Two layers of cotton clothing
		Bare		14 L 40 min	0 0066		
	5	Over cloth	8	14 L 40 min	0 0082	S 9/29/17	Two layers of cotton clothing
		Bare		14 L 40 min	0 0092		
	6	Over cloth	8	14 L 40 min	0 0286	S 10/ 2/17	Two layers of cotton clothing
		Bare		14 L 40 min	0 0189		

Infants

	No	Age, Mos	Wt Kg	Rect Temp, C	Room Temp, C	Chest	Gm H_2O per 37 5 Sq Cm	Gm H_2O per Sq dm per Hr	Rate	Diagnosis	Remarks
C	1	11	10	39	23 5	Clothed	0 0361	0 1440	14 L 40 min	Acute otitis media	Somewhat restless
						Bare	0 0304	0 1220			Quiet
	2a	8	4 5	37	23 5	Clothed	0 0826	0 3304	14 L 40 min	Convalescent from gastro enteritis	Quiet
						Bare	0 0005	0 2420			Quiet
	2b	8	4 5	37	24 5	Clothed	0 0693	0 2772	14 L 40 min		Quiet
						Bare	0 0488	0 1952			Quiet
	2c	8	4 5	37	25 5	Clothed	0 1026	0 4104	14 L 40 min		Quiet
						Bare	0 0692	0 2768			Slightly fretful

worn for eight hours) there was usually somewhat more moisture given off from the clothed than from the bare chest (Table 3C)

The fact that the infants frequently became fretful, or the occurrence of slight regurgitations of stomach contents, etc, made it necessary to reject a considerable number of observations The observations on the infant in No 2, though she was much underweight, were selected to show the effect of clothing in the absence of restlessness and other disturbing factors

It does not seem improbable that the greater amount of moisture given off from the clothed, as compared with the unclothed chest, where such was the case, can be accounted for by the increase of skin surface temperature[1] due to the clothing

In order to determine whether the clothing (as used in Table 3B) itself might give up moisture, we made determinations by placing the metal box over the clothing which was lying on a glass plate The accompanying Table 4 shows the very low values thus obtained

TABLE 4—Tests of Clothing Alone

No	Surface	Rate	Values in Grams	Kind of Clothing
1	Over plate glass	14 L 40 min	0 0040	Two layers of cotton clothing as in Table 3B
2	Over plate glass	14 L 40 min	0 0011	Two layers of cotton clothing as in Table 3B
3	Over plate glass	14 L 40 min	0 0019	Two layers of cotton clothing as in Table 3B
4	Over plate glass	14 L 40 min	0 0007	Two layers of cotton clothing as in Table 3B

It was desired, furthermore, to see how easily moisture passes through the clothing A wire mesh was placed over a shallow vessel which was filled with water to within an inch of the top Two layers of cotton clothing such as used in the experiments were spread on this mesh and the metal box placed over the clothing, then the determination was made of the amount of moisture given off in the first forty minutes Thirty minutes after the completion of this determination (seventy minutes after the clothing was placed over the vessel) a similar determination was made Table 5 shows the results of this experiment

The metal box was placed on wire mesh over the vessel of water and a determination was made, then the two layers of clothing were placed on the mesh, the metal box placed over the clothing and another determination made Table 6 shows the result

TABLE 5—TESTS OF CLOTHING PLACED OVER WATER

Surface	Hrs Clothing on	Rate	Values	Kind of Clothing
Over dish of water	Immediately	14 L 40 min	0 0745	Two layers of cotton clothing as in Table 3B
Over dish of water	After 1 hour 10 min	14 L 40 min	0 0733	Two layers of cotton clothing as in Table 3B

TABLE 6—ANOTHER DETERMINATION OVER WATER WITH AND WITHOUT CLOTHING

Surface	Hrs Clothing on	Rate	Values	Kind of Clothing
On wire mesh 1 in above water, no clothing		14 L 40 min	0 0430	
Same over clothing	Immediately	14 L 40 min	0 0389	Balbriggan undershirt and cotton shirt

From these observations it may be concluded that this particular clothing, when worn for a number of hours, is little if any bar to water vapor loss

Whether or not the humidity of the room air exercises an influence we cannot say Our data do not permit us to draw any conclusions and we therefore omitted figures for the relative humidity from our tables Niemann[5] seems to be the only one attributing a marked effect of the humidity of the air on the insensible perspiration of water from lungs and skin, while Nuttall[6] maintains that a variation in the percentage of relative humidity of the air has very little effect This question is by no means settled, it is of great importance, but must be left to special investigation

ATROPHIC INFANTS

In some observations on atrophic infants we found higher values for insensible perspiration than those obtained on convalescents under approximately equal conditions of room temperature, humidity and rate of ventilation

Niemann[5] had found the total water vapor loss (that of the skin and lungs together) greater in atrophic than in normal infants This falls in line with the observations of Schlossmann,[7] Bahrdt and Edelstein,[8] and Murlin and Hoobler,[9] which show that the metabolism of

5 Niemann Ergebn der inn Med u Kinderh, 1913, **11**, 32
6 Nuttall Arch f Hyg, 1895, **23**, 184
7 Schlossmann Ztschr f Kinderh, 1912-1913, **5**, 227
8 Bahrdt and Edelstein Festschrift Dr Otto Heubner Berlin, 1913
9 Murlin and Hoobler Am Jour Dis Child, 1915, **9**, 81

atrophic infants proceeds at a higher level, and with the observations of McClure and Sauer[1] that atrophic infants may have a high surface temperature

It is self-evident from the foregoing that we are as yet far from being able to assign to insensible perspiration of water from the skin of the infant the rôle it plays in the heat economy of the organism There is no doubt that it cannot be neglected as a factor of heat elimination, and, what is perhaps of special significance, some of the data given indicate that this mechanism possesses a rather great degree of elasticity It would seem adapted to replace some of the other means of heat elimination, if that became necessary, particularly in the non-perspiring infant

TABLE 7—DETERMINATIONS IN ATROPHIC INFANTS

No	Age Mos	Wt, Kg	Rect Temp, C	Room Temp, C	Chest	Gm H_2O per 37 5 Sq Cm	Gm H_2O per Sq dm per Hr	Rate	Diagnosis	Remarks
1	9	5 5	36 5	25 5	Bare	0 1284	0 3157	7 L 60 min	Severe atrophy	Quiet
2	2	2 5	36 0	22 0	Bare	0 0694	0 1850	7 L 60 min	Severe atrophy	Quiet
3a	6	3 5	35 5	23 0	Bare	0 0928	0 1474	7 L 60 min	Severe atrophy	Quiet
3b	6	3 5	36 0	24 0	Bare	0 0847	0 2258	7 L 60 min	Severe atrophy	Quiet

SUMMARY

In so far as determinations of the loss of water vapor from a restricted skin area permit of conclusions with regard to the loss of water vapor from the skin in toto, it appears

1 The rate of ventilation has a decided effect on the amount of water vapor given off by the skin This amount increases with the rate of ventilation up to a certain point, when it seems that a cooling effect prevents a further increase

2 Cotton garments, such as used in our experiments, do not seem to offer any obstacle to the loss of water vapor from the skin, at least not when they have been in contact with the skin a number of hours

3 Such factors as fretfulness, crying and increase in the room temperature increase the insensible perspiration of the infant

4 The loss of water vapor from the skin of certain atrophic infants is relatively great

5 The loss of water vapor from the skin seems sufficiently great to make it an important factor in the heat elimination of the infant Furthermore, this mechanism of heat elimination seems to possess a great degree of elasticity

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THE SUPERIORITY OF INOCULATIONS WITH MIXED TRIPLE VACCINE (B TYPHOSUS, B PARA-TYPHOSUS A, AND B PARA-TYPHOSUS B)

OVER SUCCESSIVE INOCULATIONS WITH THE SINGLE VACCINES, AS SHOWN BY AGGLUTININ CURVES IN MEN AND RABBITS *

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At present the subject of immunity against the enteric fevers, that is, typhoid, paratyphoid A and paratyphoid B, is of the utmost importance Records of the Franco-German War, of the Boer War,[1] of the Russo-Japanese War[2] and of the Spanish-American War[3] clearly show that the number of deaths from enteric fevers in those wars was approximately half of that due to wounds Therefore, the problem of producing immunity against the enteric fevers has occupied the minds of many investigators The success of the work done by Wright, Kabeshima[2] and others in regard to immunity against typhoid fever has been admirably demonstrated by its practical application in the armies of the United States, of Japan and of all the countries now at war (1917) It may safely be stated that since prophylactic vaccination against typhoid fever has been made more or less universal among armies, the losses from that disease have became practically negligible [4]

During the present war the paratyphoid infections have assumed the preeminent place formerly held by typhoid, and consequently investigations were necessary to place these, likewise, under control by prophylactic vaccination Castellani,[5] Cummins and Cumming,[6] Kabe-

* Alvarenga Prize Essay, 1917 Submitted for publication Sept 1, 1917

1 Osler, Sir William Bacteria versus Bullets in Boer War

2 Kabeshima T Ueber Typhus—und Paratyphus schutz-impfung mittels gemischter Typhus—und Paratyphus-vaccine und die Ergebnisse der Schutzimpfung in der Kaiserliche Japanischen Marine, etc Centralbl f Bakteriol, etc, Orgl, 1914, **74,** 294

3 Russell, F F Am Jour Med Sc, 1913, **146,** 803

4 McQueeney, E J Immunity against Infectious Disease, with Special Reference to Antityphoid Inoculation Lancet, London, 1915, **1,** 265

5 Castellani Brit Med Jour, 1916, **1.**

6 Cummins, S L, and Cumming, C C Experiments on Immunization against Bacillus Paratyphosus A Jour Royal Army Med Corps, **21,** 282

shima,[2] Vincent, Dreyer,[1] Ainley Walker,[8] and others, have demonstrated the advantages of prophylactic vaccination with combined typhoid, paratyphoid A and paratyphoid B vaccines Kabeshima[2] has not only shown that simultaneous inoculation with a vaccine containing equal parts of *B typhosus, B paratyphosus A and B paratyphosus B* produced immunity against these three infections in man and animals, but he has also proved that the reaction to this so-called "triple vaccine" was not more severe than that due to typhoid vaccine alone One of the problems in relation to prophylactic inoculation against the enteric fevers is whether or not a better immunity against these infections is obtained by inoculating with the three micro-organisms simultaneously, or by immunizing with each bacillus separately by means of a succession of inoculations, and in the latter case whether anything depends on the order in which the vaccines are introduced It is in regard to this question as well as in regard to the course of the immunity (as measured by agglutinins) produced by prophylactic enteric vaccination, that, at Prof George Dreyer's suggestion, I have performed, under the supervision of Dr E W Ainley Walker, a series of immunization experiments in men and animals with *B typhosus* and the paratyphoid bacillus

It seemed probable that the alterations which occur in the amount of agglutinins present in the blood during different periods and modes of immunization could be made to yield fresh and valuable information as to what is taking place in the organism during immunization Moreover, it was of considerable economic and general interest to ascertain as exactly as possible at what period the greatest amount of antibody is found present in the blood of inoculated animals

For these reasons I carried out a series of inoculations in a number of men and rabbits with vaccines prepared from cultures of one, two or all three of the bacilli (*B typhosus, B paratyphosus A* and *B paratyphosus B*), varying the order of their introduction in the successive immunizations of different groups of rabbits

The arrangement of these groups is shown in Table 1, where the nature of the vaccine used on each occasion, the dosage and the intervals of time between successive inoculations are given Reference is also made in each case to the corresponding agglutinin curve of the serum

The object in view in Group I was to determine the amounts of agglutinins for each micro-organism produced by simultaneous inoculations with all three bacilli, namely, *B tyhosus, B paratyphosus A* and *B paratyphosus B*

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7 Dreyer, G Hospitalstid, 1906, Ibid, Brit Med Jour, 1904, **2,** 564, Ibid, Jour Pathol and Bacteriol, 1909, **13,** 332

8 Dreyer, Ainly Walker and Gibson Lancet, London 1915, **1,** 324

TABLE 1—SCHEME OF EXPERIMENTS ON RABBITS (INTRAPERITONEAL INOCULATIONS)

Title of Experiment	Bacilli Inoculated	Fourth Day, Millions	Fifteenth Day, Millions	Seventieth Day, Millions	Eightieth Day, Millions
Group I Curves 1 and 2 Rabbits 1 and 2	B typhosus	1,000	2,000	None	None
	B paratyphosus A	500	1,000	None	None
	B paratyphosus B	500	1,000	None	None
Group II Curves 3 and 4 Rabbits 3 and 4	B typhosus	None	None	1,000	2,000
	B paratyphosus A	500	1,000	None	None
	B paratyphosus B	500	1,000	None	None
Group III Curves 5 and 6 Rabbits 5 and 6	B typhosus	1,000	2,000	None	None
	B paratyphosus A	None	None	500	1,000
	B paratyphosus B	None	None	500	1,000
Group IV Curves 7 and 8 Rabbits 7 and 8	B typhosus	None	None	1,000	2,000
	B paratyphosus A	None	None	500	1,000
	B paratyphosus B	None	None	500	1,000
Group V Curves 9 and 10 Rabbits 9 and 10	B typhosus	500	None	None	None
	B paratyphosus A	250	None	None	None
	B paratyphosus B	250	None	None	None

The aim in Group II was, first, to determine the amounts of agglutinins produced by simultaneous inoculations with *B paratyphosus A* and *B paratyphosus B*, and secondly, to ascertain the effect of subsequent inoculation with *B typhosus* (after an interval of seven weeks)

The object aimed at in Group III was, first, to determine the amounts of agglutinins produced by inoculations with *B typhosus*, and second, to ascertain the effect of subsequent simultaneous inoculations with *B paratyphosus A* and *B paratyphosus B* (after an interval of seven weeks) Thus the procedure was exactly the reverse of that in Group II

The aim in Group IV was to determine the amounts of agglutinins produced by simultaneous inoculations with *B typhosus*, *B paratyphosus A* and *B paratyphosus B* The procedure was the same as in Group I, except that the inoculations were made at a later date, being carried out on the same days as the second series of inoculations in Groups II and III

The aim in Group V was to determine the amounts of agglutinins produced by a simultaneous inoculation with *B typhosus B para-*

typhosus A and *B paratyphosus B* in a dose of half the amount used in the first doses in Groups I and IV, and of the same amount as used in the first doses of Groups VI and IX in the curves for men

In order that the results of all the experiments might be comparable, Group I received its inoculations on the same days as the first series of inoculations in Groups II and III, and Group IV received its inoculations on the same days as the second series of inoculations in Groups II and III

As soon as the foregoing experiments were fully in train, and facility had been acquired in the use of the methods involved, I instituted an investigation along similar lines in man

For this purpose I availed myself of the kindness of a number of friends who willingly placed themselves at my disposal for inoculation and repeated blood examinations To them I am deeply indebted for the opportunity of extending this investigation to the human subject, and examining in detail the development of agglutinins in man in response to immunization

The experiments in man may be divided into eight groups (that is, Groups VI-XIII) Tables 2 and 3 exhibit the details of the grouping, together with the dosage and character of the vaccine used on each occasion and the intervals between the doses Reference is also given in each case to the corresponding agglutination curve of the serum

TABLE 2—Scheme of Experiments on Men (Subcutaneous Inoculation)

Title of Experiment	Bacilli Inoculated	Third Day, Millions	Thirteenth Day, Millions	Thirty-sixth Day, Millions	Forty-sixth Day, Millions
Group VI Curves 11 and 12 V G and J G J	B typhosus	500	1,000	None	None
	B paratyphosus A	250	500	None	None
	B paratyphosus B	250	500	None	None
Group VII Curves 13 and 14 R D R and H W T	B typhosus	None	None	500	1,000
	B paratyphosus A	250	500	None	None
	B paratyphosus B	250	500	None	None
Group VIII Curves 15 and 16 T P and E A W	B typhosus	500	1,000	None	None
	B paratyphosus A	None	None	250	500
	B paratyphosus B	None	None	250	500
Group IX Curves 17 and 18 F H M and W C C	B typhosus	None	None	500	1,000
	B paratyphosus A	None	None	250	500
	B paratyphosus B	None	None	250	500

TABLE 3—SCHEME OF EXPERIMENTS ON MEN *

Title of Experiment	Bacilli Inoculated	Previous Typhoid Immunization, Millions	One to Three Years Later, Millions	Eighteen Days Later, Millions
Group X Curves 19, 20, and 21 J W, E F H and E H N	B typhosus	(1) 500 (2) 1,000 (3) 1,000	500	1,000
	B paratyphosus A	None	250	500
	B paratyphosus B	None	250	500
Group XI Curves 22 and 23 A D G and W C D	B typhosus	(1) 500 (2) 1,000 (2) 1,000	500	1,000
	B paratyphosus A	None	500	1,000
	B paratyphosus B	None	500	1,000

* These represent the intervals and doses of the majority of the individuals The exact intervals and doses are given for each case under the individual curves

The object in view in Groups VI-IX (Curves 11-18) was the same as that which has already been outlined for Groups I-IV in the series of rabbits, except that the doses used in the human subject were only half the amounts used for the rabbits

The aim in Group X was to determine the amounts of agglutinins and the effect produced by simultaneous inoculations with *B typhosus, B paratyphosus A* and *B paratyphosus B* in individuals immunized at least a year previously with two and three inoculations of *B typhosus*

Group XI differs from Group X only in that the individuals received larger doses of *B paratyphosus A* and *B paratyphosus B* after having been inoculated at least a year previously with typhoid vaccine The aim in Group XI was to determine how the production of agglutinins was affected by this increased dosage

It is generally agreed that the agglutinins produced by typhoid and paratyphoid inoculations are at any rate a rough measure of the degree of immunity induced against infection by these organisms [9] No evidence has hitherto been recorded, so far as my knowledge goes, which would tend to demonstrate the possibility of the production of antibodies without a corresponding development of immunity Moreover, it is known that in other cases (for example, that of diphtheria antitoxin) immunity may persist for a considerable period after all measurable amounts of antibodies have disappeared from the serum

Accordingly, it is, in the present state of knowledge, assumed with confidence that the measure of agglutinins present in the serum forms

9 Castellani Ztschr f Hyg, 1902, p 1, Ibid, Centralbl f Bakteriol, 1909, Ibid, Brit Med Jour, 1913, **2**, 1577, 1914, **2**, 814, 1915, **2**,, 1916, **1**.

a conservative estimate of the degree of immunity acquired, and it is further assumed that an active increase or decrease in the agglutination titer of the serum is an indication of an increase or decrease in immunity

It is not the purpose of the present investigation to inquire in detail into the nature of the processes involved in agglutination Nevertheless, a brief summary of the work done along this line may be of value in helping to throw light on the bearing of the experiments here recorded

Nearly twenty years ago it was shown by Nicolle[10] that the agglutination of bacteria depended on the formation of a compound between the agglutinating agent, or agglutinin, of the serum, and the agglutinable substance in the bacteria After Bordet[11] and later Joos[12] had proved that the presence of salt is essential for agglutination, it has been customary to regard the process as a direct or indirect consequence of the union of these three substances (that is, salt, agglutinin and agglutinable substance) Gruber,[13] Neufield,[14] Bordet,[11] Ehrlich, Wassermann,[15] Kirstein, Bail,[16] Eisenberg,[17] Volk, Dreyer and Jex-Blake,[18] Ainley Walker[19] (1902), Dreyer and Ainley Walker[20] (1909) have all greatly advanced our knowledge of the essential characteristics of this process, and Ainley Walker[19] and later Dreyer and Ainley Walker,[20] and more recently McFarland[21] (1911), have shown that agglutinins are produced by the leukocytes and leukocyte-forming tissues of the body (notably the bone marrow)

It thus appears that the production of agglutinins is in close association with those tissues of the body whose activity appears to form the basis for the development of immunity

METHODS

The vaccines used in these experiments were kindly made for me by Dr E W Ainley Walker, from stock cultures of *B typhosus, B paratyphosus A* and *B paratyphosus B,* grown on agar slopes in culture tubes for twenty-four

10 Nicolle Ann de l'Inst Pasteur, 1898, **12,** 161, Nicolle and French Ibid, 1902, **16,** 562

11 Bordet Ann de l'Inst Pasteur, 1896, **10,** 193, Ibid, 1900, **14,** 257

12 Joos Ztschr f Hyg u Infectionskrankh, 1901, **36,** 422, Ibid, 1902, **40,** 203

13 Gruber Munchen med Wchnschr, 1899, **46,** 1329

14 Neufeld Ztschr f Hyg u Infectionskrankh, Leipsic, 1902, **40,** 54

15 Wassermann Ztschr f Hyg u Infectionskrankh, 1902, **42,** 267

16 Bail Prag med Wchnschr, 1901, **26,** 85

17 Eisenberg Ztschr f Hyg u Infectionskrankh, 1902, **40,** 155

18 Dreyer, G, and Blake, Jex A Jour Path and Bacteriol, January, 1906, p 1

19 Ainley Walker, E W Jour Hyg, Cambridge, 1903, **3,** 52

20 Dreyer and Ainley Walker Jour Pathol and Bacteriol, 1909, **14,** 28

21 McFarland, W S Communications de L'Institut Sciothiapigne de L'Etat Danois

hours at 37 C The growth was then washed off with normal saline solution to which 0.5 per cent. of phenol had been added. Each bacillary suspension was killed by heating in a waterbath at 56 C for thirty minutes, then gradually raising the temperature to 56 C and maintaining it at that level for an hour. The suspensions were then proved sterile and counted by Wright's blood-film method. One vaccine was then made so that 1 c.c. contained 1,000 million *B. typhosus*. A second vaccine containing 500 million *B. paratyphosus A*, and 500 million *B. paratyphosus B* in 1 c.c., and a third vaccine containing 1,000 million *B. typhosus*, 500 million *B. paratyphosus A*, and 500 million *B. paratyphosus B* in 1 c.c. were made. In order that Castellani's results might be repeated, a fourth vaccine was made containing 1,000 million *B. typhosus*, 1,000 million *B. paratyphosus A* and 1,000 million *B. paratyphosus B* in 1 c.c.

The vaccines were distributed into small sterile glass vials and sealed up and kept in a cold store at 2 C until required. One or two bottles from each batch were then finally tested for sterility by culture methods and also by injecting 2 c.c. into a rabbit and a guinea-pig.

The inoculation was made in the case of two rabbits (Group V) by intraperitoneal injections of 0.5 c.c. of vaccine. But as this proved to be too small a dose with which to demonstrate agglutinin curves clearly, it was decided to give all of the other rabbits intraperitoneal injections of 1 c.c. followed in from nine to fifteen days later by a second dose of 2 c.c. In the case of the men, 0.5 c.c. of the vaccine, followed at an interval of from nine to twenty days by 1 c.c., was injected subcutaneously at the back of the arm with the usual precautions.

For each test from 1 to 2 c.c. of blood was taken. In the case of the rabbit it was procured by the following routine: the ear was shaved, then sharply flicked and a few drops of xylol were dropped on it to dilate the vessels. A small amount of petrolatum was rubbed on the area over the vessel, which was then punctured with a sterilized needle and the blood was allowed to drop into a small sterile test tube. In the case of the men from 1 to 2 c.c. of blood was usually collected by inserting a small sterilized hypodermic needle into the median basilic vein at the bend of the elbow (the skin having been previously painted with iodin) and the blood was aspirated into a sterile syringe. The blood was then blown into a small sterile test tube. In a few instances blood was obtained by pricking the thumb or finger and collecting the blood in a Wright's capsule or in the ingenious and efficient Asheville capsule described by Lyon.[22] In practice, when frequent bleedings are necessary, the former technic is preferable, for it is simpler and causes far less discomfort to the subject.

The blood thus collected is allowed to clot for an hour at room temperature. The clot is then loosened from the sides of the tube with a fine glass rod and the tube is placed in a cold store at 2 C until tested. I have found that tests of the same serum at different periods within forty-eight hours give no appreciable change, but keeping for a longer time gives less accurate observations.

The tubes are then centrifuged for several minutes and the supernatant serum pipetted off and tested by Dreyer's[7] technic.

The description which follows is that issued by the Standards Laboratory of the Department of Pathology of this university on behalf of the Medical Research Committee.

1. *Technic*.—Take a stand containing fifteen agglutination tubes in three rows of five each, and a dilution tube.

With the proper dropping pipet measure out into the dilution tube 30 drops of normal saline solution (0.85 per cent. sodium chlorid, in distilled water, where the water supply is pure, tap water can be used instead of saline solution), by means of gentle pressure on the teat.

Wash the pipet with distilled water.

22. Lyon, Jr., M. W.: Jour. Am. Med. Assn., 1915, **65**, 1813.

Dry out the pipet with successive quantities of absolute alcohol, followed by successive quantities of ether, and get rid of the ether

Take up the serum to be tested into the dried pipet For the first examination measure out 30 drops of the serum into the dilution tube already containing the 30 drops of saline solution, thus obtaining a dilution of 1 in 2 Mix thoroughly

Carefully wash out the pipet

With the pipet measure out into each row of tubes as follows

No of Tube	Drops of Normal Saline Solution	Drops of Serum Dilution 1 in 2	
1	0	10	To each tube in Row 1 add 15 drops of *B typhosus* standard agglutinable culture
2	5	5	
3	8	2	To each tube in Row 2 add 15 drops of *B paratyphosus A* standard agglutinable culture
4	9	1	
5	10	0	To each tube in Row 3 add 15 drops of *B paratyphosus B* standard agglutinable culture

At each stage of the procedure the pipet is carefully washed and dried out with successive quantities of absolute alcohol followed by successive quantities of ether

Shake each tube thoroughly in order from right to left, that is, beginning each row with the highest dilution

Place the stand either for two hours in a water-bath at from 50 to 55 C (not in dry air), or for eight hours in an incubator at 37 C if traces of hemolysis are present[23]

In Tube 1 of each row the serum acts in a dilution of 1 in 5
In Tube 2 of each row the serum acts in a dilution of 1 in 10
In Tube 3 of each row the serum acts in a dilution of 1 in 25
In Tube 4 of each row the serum acts in a dilution of 1 in 50

Tube 5 containing no serum, is the control against spontaneous agglutination

If the limit of agglutination is not reached within this series, higher dilutions are followed out in a similar manner

Thus, for example, 57 drops of normal saline solution plus 3 drops of a 1 in 10 serum dilution will give a serum dilution of 1 in 200, and, using the same quantities as before, one has the serum acting in dilutions of 1 in 500, 1 in 1,000, 1 in 2,500, and 1 in 5,000 And similarly for higher dilutions

The tubes are examined after two hours at from 50 to 55 C, or eight hours at 37 C, followed by standing at room temperature for fifteen minutes The reading is taken by comparing each tube in succession with the control tube, and is preferably made by means of artificial light against a black background

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23 In the case of the rabbit's serum, I found that hemolysis was slightly more frequent than in human serum, so I tested all of the former in the incubator at 37 C for eight hours, while all of the latter I examined in the more usual way in the water bath at from 50 to 55 C for two hours I may say that in several experiments in which I tested one sample of the same serum in the water bath at 55 C for two hours, and a second sample in the incubator at 37 C for eight hours, I found no discrepancy or difference in the titer of agglutination produced so the results of the two procedures are comparable in every way

If daylight is used, the tubes inspected should be partly shadowed by passing a finger up and down behind them

The highest dilution in which marked agglutination (medium sized flocculi) without sedimentation can be detected by the naked eye is "standard agglutination"

It frequently happens that in a given series there is no tube which shows a degree of agglutination which we can accept as "standard" (S) For instance there may be a jump from total (T) in one tube to trace (tr) in the next—the serum in the former is too strong, that in the latter too weak to produce standard (S) agglutination Evidently standard (S) agglutination would be given in a serum dilution intermediate between these two How are we to judge where to "place" our standard? Experience shows that all the recognizable degrees of agglutination, from total to trace, may be tabulated as in the following scheme

T = Total—complete agglutination, the supernatant fluid being absolutely clear and all of the bacteria being in the sediment at the bottom of the tube
T = a point midway between T and T—
T— = Total Minus—supernatant fluid contains large flocculi and sedimentation is also present
T— = a point midway between T— and S+
S+ = Coarse Standard—*large* flocculi *without* sedimentation
S+ = a point midway between S+ and S
S = Standard—*medium* flocculi *without* sedimentation
S = a point midway between S and S—
S— = Fine Standard—*fine flocculi without* sedimentation
S— = a point midway between S— and tr+
tr+ = Trace Plus—agglutination *plainly* visible to naked eye but not sufficiently well marked to see separate flocculi
tr = Trace—agglutination just visible to the naked eye

This scheme shows 12 degrees of agglutination which may bridge the space between total and trace at equal intervals Such a scheme makes it easy to calculate the probable position of standard agglutination when it falls between two tubes For instance, on the twenty-eighth day of Curve 12 I found that the typhoid agglutination in the series of tubes was as follows

Tube 1	Tube 2
$\frac{1}{2{,}500}$ T	$\frac{1}{5{,}000}$ S—

Tube 1 shows more than standard agglutination and Tube 2 shows less than standard Standard, therefore, must lie between Tubes 1 and 2, that is, between the dilutions $\frac{1}{2{,}500}$ and $\frac{1}{5{,}000}$ Assuming that the gradations in the scheme I have adopted are equal, since eight of these gradations occur between T and S—, then S would be placed as follows

	1	2	3	4	5	6	7	8
T $\frac{1}{2{,}500}$	*T*	T—	*T*—	S+	*S*+	S $\frac{1}{4{,}375}$	*S*	S— $\frac{1}{5{,}000}$

In other words, the dilution in which standard agglutination would occur is $\frac{1}{2{,}500}$ + $\frac{6}{8}$ of the difference between $\frac{1}{2{,}500}$ and $\frac{1}{5{,}000}$, that is, $\frac{1}{2{,}500}$ + $\frac{6}{8}$ of $\frac{1}{2{,}500}$, that is, $\frac{1}{2{,}500}$ + $\frac{1}{1{,}875}$, that is, $\frac{1}{4{,}375}$ (when divided by the sensitivity factor of the agglutinable culture used, this equalled 541 "standard agglutinin units")

This arbitrary system may lead to slight error, but as it has the great advantage of being applicable to all cases and does not depend on any bias of the experimenter, I have adopted it

When the standard degree of agglutination ("standard agglutination") occurs with standard agglutinable culture in a serum dilution of 1 in x, then x divided by the figure given on the label (sensitivity factor) of the standard agglutinable culture employed gives the number of "standard agglutinin units" contained in 1 c c of the serum examined[24]

Thus, if standard agglutination occurs in a dilution of 1 in 1,000 and the number on the label is 2 5, then $\frac{1,000}{2\ 5}$, that is, 400, is the number of standard agglutinin units contained in 1 c c of the serum examined

For uniformity and simplicity in recording results they should be expressed in standard agglutinin units

In the curves the ordinates represent the number of standard agglutinin units The abscissae represent the days on which examinations were made

The standardized agglutinable cultures used in this technic were those prepared by the standards laboratory of the Department of Pathology, Oxford, on behalf of the Medical Research Committee, and the description I have given of their mode of preparation and standardization is the one issued by that laboratory

1 *Preparation*—The bacillus (*B typhosus, B paratyphosus*, etc) is grown for twenty-four hours at 37 C in ordinary veal peptone bouillon[25] in large Erlenmeyer flasks partly filled (1 liter of bouillon in a one and a half liter flask)

Before use the flasks of bouillon are sterilized in the autoclave at 115 C for not more than fifteen minutes, and are then tested for sterility by incubation at 37 C for forty-eight hours

They are inoculated with a few drops each from a twenty to twenty-four hours' old bouillon culture of the bacillus (*B typhosus* or *B paratyphosus*, etc)

The culture used should be one which has been subcultivated daily in bouillon for one or two weeks (or longer) This continued subcultivation has the effect of increasing its agglutinability and diminishing any tendency to spontaneous agglutination

At the end of twenty to twenty-four hours' growth at 37 C the flasks are well shaken, and to each is added 0 1 per cent (1 c c per liter) of commercial (40 per cent) formaldehyd They are again shaken and placed in a cold chamber in the dark at about 2 C

At intervals on the same day and on subsequent days for four or five days the flasks are again thoroughly shaken and replaced at once in the cold chamber

After three or four days they will be found to be absolutely sterilized Should it happen that the bacterial suspension is not entirely homogeneous, it may be shaken for some hours in a mechanical shaker, or may finally be filtered through sterile cotton wool

2 *Standardization*—The process of standardization consists (*a*) in making up the killed culture to an opacity as nearly as possible identical with that of the standard agglutinable culture, (*b*) in measuring its agglutinability as compared with the standard agglutinable culture by the use of standard serum

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24 The standard agglutinin unit is that amount of agglutinating serum which when made up to 1 c c volume with normal saline solution causes standard agglutination on being mixed with 1 5 c c of a particular standard agglutinable culture and maintained at 55 C for two hours in a water bath, or at 37 C for eight hours in an incubator, followed by fifteen minutes at room temperature

25 The bouillon is titrated against phenolphthalein and two-thirds of that amount of sodium hydrate which would render it neutral to phenolphthalein is added before the final boiling and filtration

(*a*) The killed culture is diluted to the required degree with normal saline solution, to which has been added 0.1 per cent of commercial formaldehyd

In making up the standard agglutinable culture issued, a constant opacity is secured by the use of a special apparatus (the diaphanometer)[26] But for ordinary purposes it will be found that reasonable accuracy is obtained by putting a measured quantity of killed culture and of standard agglutinable culture in two tubes of equal size and diameter and comparing the opacity against thin black lines ruled on a white background Diluting fluid is added until the opacity of the killed culture is brought down to that of the standard agglutinable culture The quantity of fluid thus added being known, the amount of diluting fluid which must be added to the killed cultures is readily calculated

(*b*) To measure the agglutinability of the killed culture thus diluted, proceed as follows

Take two stands and place twelve agglutination tubes in each Prepare (1) a dilution of standard agglutinating serum of such strength that each cubic centimeter contains from 4 to 8 standard agglutinin units, and from this prepare (2) a second dilution of half that strength

With the pipet measure out

	Drops of Normal Saline Solution	Serum Dilution
Into Tube 1 of each stand	0	10 drops of Dilution 1
Into Tube 2 of each stand	2	8 drops of Dilution 1
Into Tube 3 of each stand	4	6 drops of Dilution 1
Into Tube 4 of each stand	5	5 drops of Dilution 1
Into Tube 5 of each stand	6	4 drops of Dilution 1
Into Tube 6 of each stand	3	7 drops of Dilution 2
Into Tube 7 of each stand	4	6 drops of Dilution 2
Into Tube 8 of each stand	5	5 drops of Dilution 2
Into Tube 9 of each stand	6	4 drops of Dilution 2
Into Tube 10 of each stand	7	3 drops of Dilution 2
Into Tube 11 of each stand	8	2 drops of Dilution 2
Into Tube 12 of each stand	10	0 drops of Dilution 2

To each tube of one stand is added 15 drops of standard agglutinable culture, and to each tube of the other stand, 15 drops of the killed culture under standardization

At each stage of the procedure the pipet is carefully washed and dried out with successive quantities of absolute alcohol, followed by successive quantities of ether

The stands are placed for two hours in a water bath at from 50 to 55 C, then allowed to stand for fifteen minutes at room temperature and a reading subsequently taken by selecting in the series made with standard agglutinable culture the tube which exhibits standard agglutination (the highest dilution in which marked agglutination without sedimentation, can be detected by the naked eye), and ascertaining which tube in the other series shows the same degree of agglutination Should the tube be the same in each series the agglutinability of the killed culture is clearly equal to that of the standard If not the same, the degree of agglutinability of the killed culture is now readily determined

Thus, suppose that Tube 5 in the standard series corresponds to Tube 2 in the other series The standard agglutinable culture is twice as agglutinable

26 More recently the standards department of the Department of Pathology, Oxford University, has adopted a more simple method of standardizing the opacity of agglutinable cultures This is described by Dreyer and Gardner in *The Bio-Chemical Journal* (England), 1916 **10**, 399

as the killed culture under standardization, since only half the quantity of serum has been required to agglutinate it to the same degree

Hence, if any given serum presented for examination is found to agglutinate this particular killed culture in a dilution of, say, 1 in 500, then 500 multiplied by 2 and divided by the figure given on the label of the standard agglutinable culture is the number of standard agglutinin units in 1 c c of the serum examined

Or again, if the killed culture were, say, 1 3 times as agglutinable as the standard agglutinable culture, then in the same example as above, 500 divided by 1 3, and again divided by the figure given on the label of the standard agglutinable culture, is the number of standard agglutinin units in 1 c c of the serum examined

It will be seen from this description that the standard cultures are prepared in batches, each of which bears a different sensitivity factor by means of which the standard units are calculated In working out long curves it is seldom possible to employ the same batch of culture throughout In most of my curves one or more culture changes have been made As a rule, no appreciable irregularity in the curve is found at these points, but in one or two instances a distinct irregularity occurred which was attributed to an alteration since the time of standardization in the sensitiveness of one or other of the cultures employed When it has been perfectly clear that irregularities have been due to these changes, I have corrected the levels of the curve at these points

CURVES PLOTTED FROM THE EXPERIMENTS ON MEN AND ANIMALS

I shall first give a more or less detailed description of the curves plotted from the results of agglutination tests made at short intervals on the rabbits, and then a similar description for the curves plotted from the agglutination tests made on the human subject

The rabbits were all healthy animals They were weighed daily In each case the blood was examined two or more times before inoculations were commenced, to determine the base-line of normal agglutination The local and general reactions to the inoculations given were in no way severe At the most there was only a small decrease in body weight following the injection

Rabbit 1—(Group 1, Curve 1) *The typhoid agglutinins* began their rise on the third day from inoculation, reaching a maximum on the ninth day On the eleventh day the rapid fall of the typhoid agglutinins (33 per cent) had begun The second inoculation was then administered For the next two days there is no change in agglutination titer (that is, no negative phase[27] was

27 Any fall in titer which occurs within forty-eight hours after an inoculation, is referred to in these descriptions of curves, as a negative phase In many cases (as in falling curves) it might be contended that these drops were not the true negative phases of Wright However, their significance will be discussed later

EXPLANATION OF CURVES

▬▬▬ = typhoid ——— = paratyphoid A - - - - - = paratyphoid B

Curve 1—Group 1, Rabbit 1

Bacilli Inoculated	Fourth Day	Fifteenth Day		
B typhosus	1,000 million	2,000 million	Nil	Nil
B paratyphosus A	500 million	1,000 million	Nil	Nil
B paratyphosus B	500 million	1,000 million	Nil	Nil
Body weight	2,390 gm	2,270 gm	Nil	Nil

Curve 2—Group 1, Rabbit 2

Bacilli Inoculated	Third Day	Eighteenth Day		
B typhosus	1,000 million	2,000 million	Nil	Nil
B paratyphosus A	500 million	1,000 million	Nil	Nil
B paratyphosus B	500 million	1,000 million	Nil	Nil
Body weight	2 050 gm	1,990 gm		

Curve 3—Group 2, Rabbit 3

Bacilli Inoculated	Fourth Day	Fifteenth Day	Seventieth Day	Eightieth Day
B typhosus	Nil	Nil	1,000 million	2 000 million
B paratyphosus A	500 million	1,000 million	Nil	Nil
B paratyphosus B	500 million	1,000 million	Nil	Nil
Body weight	2,640 gm	2,250 gm	2,540 gm	2,480 gm

Curve 4—Group 2, Rabbit 4

Bacilli Inoculated	Fourth Day	Fifteenth Day	Seventieth Day	Eightieth Day
B typhosus	Nil	Nil	1 000 million	2 000 million
B paratyphosus A	500 million	1,000 million	Nil	Nil
B paratyphosus B	500 million	1,000 million	Nil	Nil
Body weight	1,480 gm	1,510 gm	1,600 gm	1,640 gm

Note Rabbit 4 developed a "wry" neck through fighting on the seventy eighth day

Curve 5—Group 3, Rabbit 5

Bacilli Inoculated	Fourth Day	Fifteenth Day	Seventieth Day	Eightieth Day
B typhosus	1,000 million	2,000 million	Nil	Nil
B paratyphosus A	Nil	Nil	500 million	1,000 million
B paratyphosus B	Nil	Nil	500 million	1,000 million
Body weight	2,060 gm	2,230 gm	2,000 gm	2,220 gm

Rabbit 5 developed a suppurating ear in the twenty second day which continued throughout the experiment

Curve 6—Group 3, Rabbit 6

Bacilli Inoculated	Fourth Day	Fifteenth Day		
B typhosus	1,000 million	2 000 million	Nil	Nil
B paratyphosus A	Nil	Nil	Nil	Nil
B paratyphosus B	Nil	Nil	Nil	Nil
Body weight	1,250 gm	1,400 gm		

Rabbit 6 died on the twelfth day with a broken neck caused by fighting

Curve 7—Group 4, Rabbit 7

Bacilli Inoculated			Second Day	Eleventh Day
B typhosus	Nil	Nil	1,000 million	2,000 million
B paratyphosus A	Nil	Nil	500 million	1,000 million
B paratyphosus B	Nil	Nil	500 million	1,000 million
Body weight			1,290 gm	1,400 gm

Curve 8—Group 4, Rabbit 8

Bacilli Inoculated			Second Day	Eleventh Day
B typhosus	Nil	Nil	1,000 million	2,000 million
B paratyphosus A	Nil	Nil	500 million	1,000 million
B paratyphosus B	Nil	Nil	500 million	1,000 million
Body weight			1,210 gm	1,270 gm

Curve 9—Group 5, Rabbit 9

Bacilli Inoculated	Ninth Day			
B typhosus	500 million	Nil	Nil	Nil
B paratyphosus A	250 million	Nil	Nil	Nil
B paratyphosus B	250 million	Nil	Nil	Nil
Body weight	1,900 gm			

Curve 10—Group 5, Rabbit 10

Bacilli Inoculated	Ninth Day			
B typhosus	500 million	Nil	Nil	Nil
B paratyphosus A	250 million	Nil	Nil	Nil
B paratyphosus B	250 million	Nil	Nil	Nil
Body weight	2,930 gm			

Curve 11—Group 6, W G

Bacilli Inoculated	Sixth Day	Fifteenth Day		
B typhosus	500 million	1,000 million	Nil	Nil
B paratyphosus A	250 million	500 million	Nil	Nil
B paratyphosus B	250 million	500 million	Nil	Nil

Curve 12—Group 6, J G J

Bacilli Inoculated	Sixth Day	Twenty First Day		
B typhosus	500 million	1,000 million	Nil	Nil
B paratyphosus A	250 million	500 million	Nil	Nil
B paratyphosus B	250 million	500 million	Nil	Nil

Curve 13—Group 7, R F D R

Bacilli Inoculated	Third Day	Thirteenth Day	Thirty Sixth Day	Forty Fifth Day
B typhosus	Nil	Nil	500 million	1,000 million
B paratyphosus A	250 million	500 million	Nil	Nil
B paratyphosus B	250 million	500 million	Nil	Nil

Curve 14—Group 7, H W T

Bacilli Inoculated	Third Day	Thirteenth Day	Thirty Eighth Day	Forty Eighth Day
B typhosus	Nil	Nil	500 million	1 000 million
B paratyphosus A	250 million	500 million	Nil	Nil
B paratyphosus B	250 million	500 million	Nil	Nil

Curve 15—Group 8, T P

Bacilli Inoculated	Third Day	Thirteenth Day	Thirty Sixth Day	Forty Fifth Day
B typhosus	500 million	1,000 million	Nil	Nil
B paratyphosus A	Nil	Nil	250 million	500 million
B paratyphosus B	Nil	Nil	250 million	500 million

Curve 16—Group 8, E A W

Bacilli Inoculated	Third Day	Thirteenth Day	Thirty Eighth Day	Forty Eighth Day
B typhosus	500 million	1 000 million	Nil	Nil
B paratyphosus A	Nil	Nil	250 million	500 million
B paratyphosus B	Nil	Nil	250 million	500 million

Curve 17—Group 9, W C C

Bacilli Inoculated			First Day	Twenty First Day
B typhosus	Nil	Nil	500 million	1,000 million
B paratyphosus A	Nil	Nil	250 million	500 million
B paratyphosus B	Nil	Nil	250 million	500 million

Curve 18—Group 9, F H M

Bacilli Inoculated			First Day	Twenty Second Day
B typhosus	Nil	Nil	500 million	1,000 million
B paratyphosus A	Nil	Nil	250 million	500 million
B paratyphosus B	Nil	Nil	250 million	500 million

Curve 19—Group 10, J W

Bacilli Inoculated	Previous Typhoid Immunization	Ten Months Later	Nineteen Days Later
B typhosus	(1) 500 million (2) 1,000 million	500 million	1,000 million
B paratyphosus A	nil	250 million	500 million
B paratyphosus B	nil	250 million	500 million

Curve 20—Group 10, E H N

Bacilli Inoculated	Previous Typhoid Immunization	Thirty Two Months Later	Forty Days Later
B typhosus	(1) 500 million (2) 1,000 million (3) 1 000 million	500 million	1,000 million
B paratyphosus A	nil	250 million	500 million
B paratyphosus B	nil	250 million	500 million

Curve 21—Group 10, E F H

Bacilli Inoculated	Previous Typhoid Immunization	Twenty Two Months Later	Nine Days Later
B typhosus	(1) 500 million (2) 1,000 million (3) 1 000 million	500 million	1 000 million
B paratyphosus A	nil	250 million	500 million
B paratyphosus B	nil	250 million	500 million

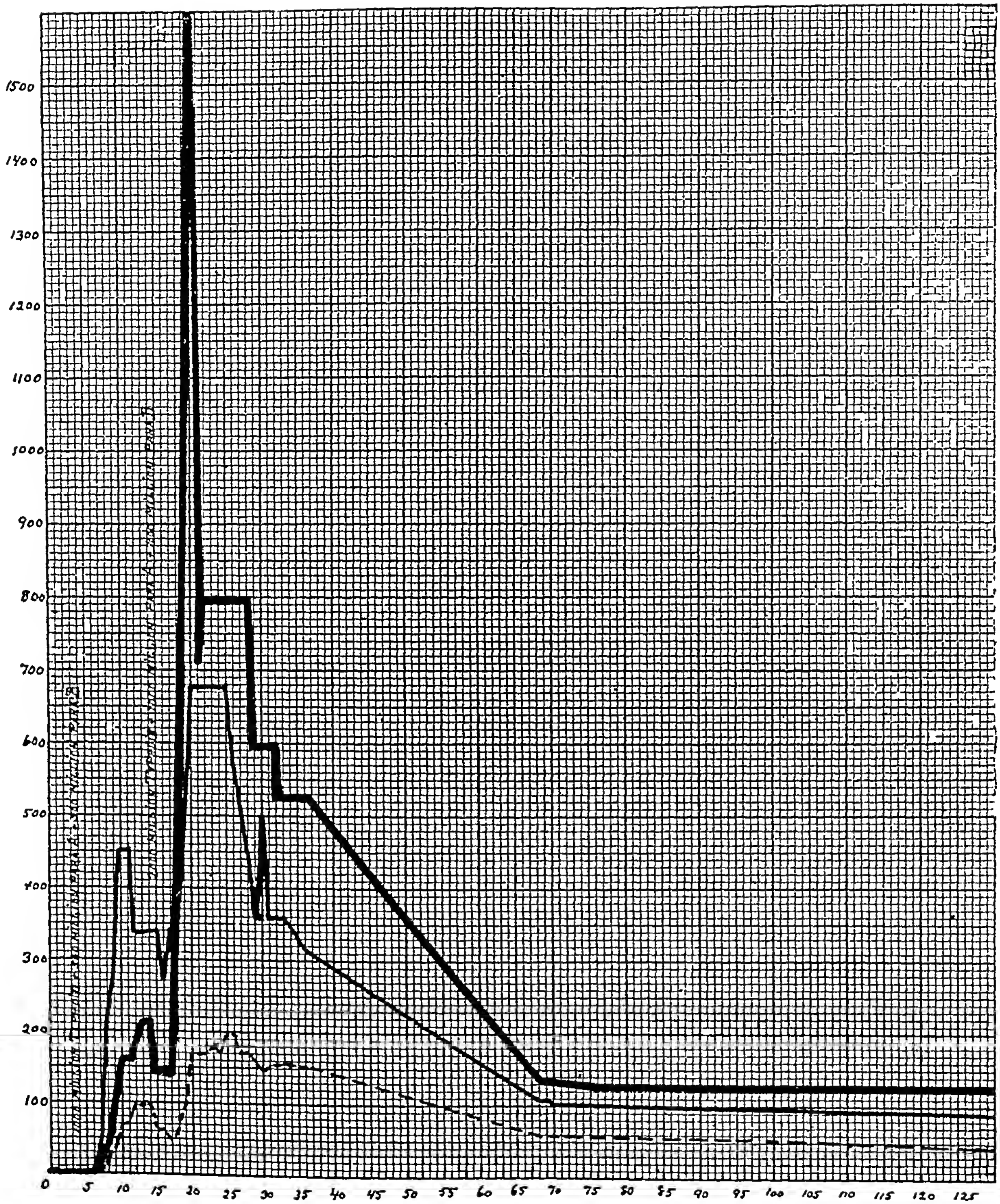
Curve 22—Group 11, A D G

Bacilli Inoculated	Previous Typhoid Immunization	Fourteen Months Later	Sixteen Days Later
B typhosus	(1) 1 000 million	500 million	1,000 million
B paratyphosus A	nil	500 million	1 000 million
B paratyphosus B	nil	500 million	1,000 million

The local and general reaction to this increased dose in curves 22 and 23 was not appreciably different from those following the more usual doses

Curve 23—Group 11, W C D

Bacilli Inoculated	Previous Typhoid Immunization	Twenty Five Months Later	Eighteen Days Later
B typhosus	(1) 500 million (2) 1,000 million (3) 1,000 million	500 million	1,000 million
B paratyphosus A	nil	500 million	1 000 million
B paratyphosus B	nil	500 million	1 000 million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Curve 1

TABLE 4—Data from which Curve 1 Was Plotted

Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	B paratyphosus A	B paratyphosus B
1	2,500	0	0	0
2	2,450	0	0	0
4	2,390	0	0	0
4	2,390	Inoculation,	1 c c T A B = {1,000 / 500 / 500	million typhoid / million para A / million para B
5	2,350	0	0	0
6	2,350	0	2 70	0
7	2,350	26 59	50 67	6 87
8	2,310	44 32	202 70	27 77
9	2,250	88 63	270 27	37 03
10	2,200	159 57	450 43	69 44
11	2,200	159 57	450 43	69 44
12	2,260	186 17	337 83	97 0
13	2,240	212 76	337 83	97 0
14	2,200	212 76	337 83	97 0
15	2,270	141 70	337 83	64 0
15	2,270	Inoculation,	2 c c T A B = {2,000 / 1,000 / 1,000	million T / million A / million B
16	2,180	141 70	270 27	62 0
17	2,200	141 70	331 83	48 0
18	2,200	354 59	337 83	62 0
19	2,120	709 14	506 75	97 0
20	2,200	1,595 74	675 68	169 0
21	2,270	709 14	675 68	169 0
22	2,190	797 87	675 68	169 0
23	2,340	797 87	675 68	180 0
24	2,190	797 87	675 68	169 0
25	2,200	797 87	675 68	193 0
26	2,150	797 87	563 06	193 0
27	2,300	797 87	506 75	169 0
28	2,200	797 87	450 43	169 0
29	2,260	595 23	357 14	159 0
30	2,390	595 23	500 17	145 0
31	2,270	595 23	357 14	152 0
32	2,220	529 1	357 14	151 0
33	2,250	259 1	357 14	159 0
36	2,280	529 1	314 28	151 1
68	2,570	134 0	107 85	36 5
69	2,490	134 0	107 14	32 64
74	2,470	129 0	100 0	50 0

TABLE 4—DATA FROM WHICH CURVE 1 WAS PLOTTED—(*Continued*)

Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	B paratyphosus A	B paratyphosus B
76	2 450	129 0	100 0	44 64
83	2,640	128 0	119 04	56 11
90	2,570	126 0	152 0	56 11
97	2,800	137 98	98 0	56 11
104	2,800	130 0	82 8	50 0
111		120 0	82 8	35 6
118	2,760	104 0	82 8	35 6
125	2,810	112 0	122 0	28 0
132	2,710	120 0	115 0	28 0
139	2,830	130 0	122 0	32 0
146		130 0	171 0	22 4
153		130 0	85 5	12 8
160		130 0	85 5	28 0
167		130 0	171 0	28 0

seen) On the next day (the third after the second inoculation, the fourteenth after the first) the new rise had commenced, for the titer was more than doubled and rapidly rose to a maximum on the fifth day (that is, the sixteenth day from the first inoculation) The next day reveals a fall of 50 per cent The titer shows but little change from this point until the twenty-fourth day (from first inoculation), when it falls gradually until the thirty-second day (from first inoculation) When next examined after an interval of thirty-two days the agglutination titer had fallen 71 per cent since the last examination (that is, the thirty-second day) Seventeen subsequent examinations covering a period of 139 days showed no further appreciable difference in agglutination titer, showing that it had reached a point that was practically equilibrium [28]

The paratyphoid A agglutinins begin their rise on the second day (the first after inoculation), reaching the maximum of the first rise on the sixth day, after which there is a rapid fall (25 per cent) The paratyphoid A curve shows no change until after the eleventh day At this point the second inoculation is given A negative phase (20 per cent) occurs on the following day From this point the new curve quickly rises (150 per cent) reaching a maximum on the fifth day after the second inoculation (the sixteenth day after the first inoculation) No change in titer is seen from the fifth to eleventh day after the second inoculation A rapid fall (50 per cent) occurs from the eleventh to seventeenth day From the seventeenth to twenty-first day (after the second inoculation) there is little change When next examined after an interval of thirty-two days, it has fallen 66 per cent As in the typhoid curve, the paratyphoid A has now reached its point of equilibrium

The *paratyphoid B agglutinins* commence their rise on the third day, reaching a maximum on the sixth This is followed by a rapid fall (33 per cent) until the second inoculation on the eleventh day The curve either continues

28 By the term equilibrium I refer to that condition in which the ratio between production and excretion of agglutinins is practically unity

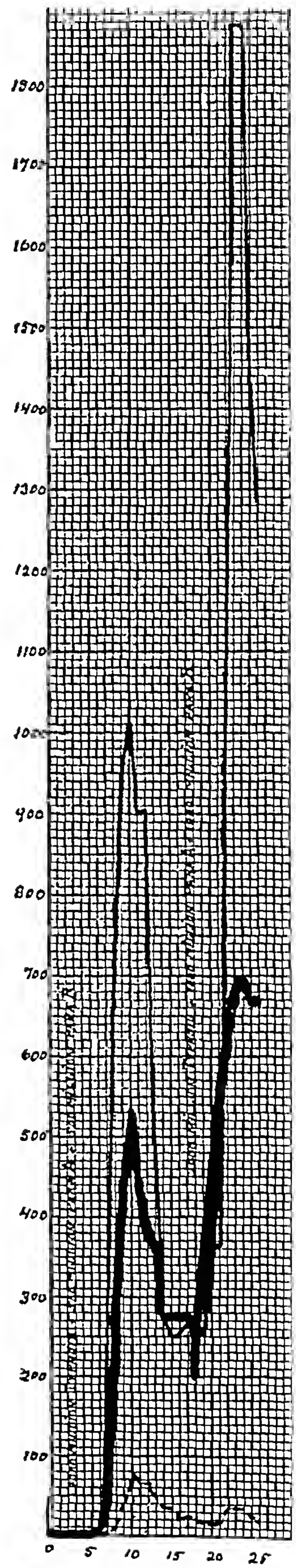
falling or a negative phase (20 per cent) is exhibited for the next two days The new rise commenced on the third day (the fourteenth from first inoculation) and reaches a maximum on the tenth day The curve then behaves in a manner similar to that of the typhoid and paratyphoid A curves[29]

Rabbit 2—(Group 1, Curve 2) *The typhoid agglutinins* commence their rise on the third day after inoculation, reaching the maximum on the seventh A rapid fall (50 per cent) follows for the next four days, after which the curve shows no change for three days, finally falling 33 per cent on the

TABLE 5—Data from which Curve 2 Was Plotted

Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	B paratyphosus A	B paratyphosus B
1		0	0	0
2		0	0	0
3	2,050	0	0	0
3	2 050	Inoculation,	1 c c T A B = {1,000 million typhoid, 500 million A, 500 million B}	
4	1,940	0	0	0
5		0	0	0
6	2,050	4 25	13 51	0
7	1,970	53 18	100 00	0
8	2,050	265 95	675 68	16 9
9	1,970	443 25	945 94	48 0
10	1,920	531 90	1,013 51	72 2
11	2,060	443 25	900 89	64 0
12	1,920	398 93	900 89	64 0
13	1,940	365 69	506 75	48 0
14		272 81	271 42	36 0
15		272 81	250 0	36 0
16	1,980	272 81	250 0	21 2
17	1,920	272 81	265 25	21 2
18	1,990	198 41	271 42	19 3
18	1,990	Inoculation,	2 c c T A B = {2,000 million T, 1,000 million A, 1,000 million B}	
19	1,895	306 63	250 0	19 3
20	1,890	277 71	357 14	17 4
21	1,960	529 1	357 14	19 3
22	1,950	595 23	1,071 42	32 0
23	1 900	661 37	1,857 42	32 0
24	1,910	694 44	1,857 42	32 0
25	1,980	661 37	1,428 57	24 0
26		661 37	1,285 71	20 5

29 For the sake of brevity typhoid and *B typhosus* will often be expressed as T, paratyphoid A and *B paratyphosus A* as A, and paratyphoid B and *B paratyphosus B* as B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Curve 2

fifteenth day At this point the second inoculation was given The curve starts its new rise the following day (no negative phase being seen), and reaches its maximum in six days (twenty-first from first inoculation), after which it falls for the next two days No further examination was made

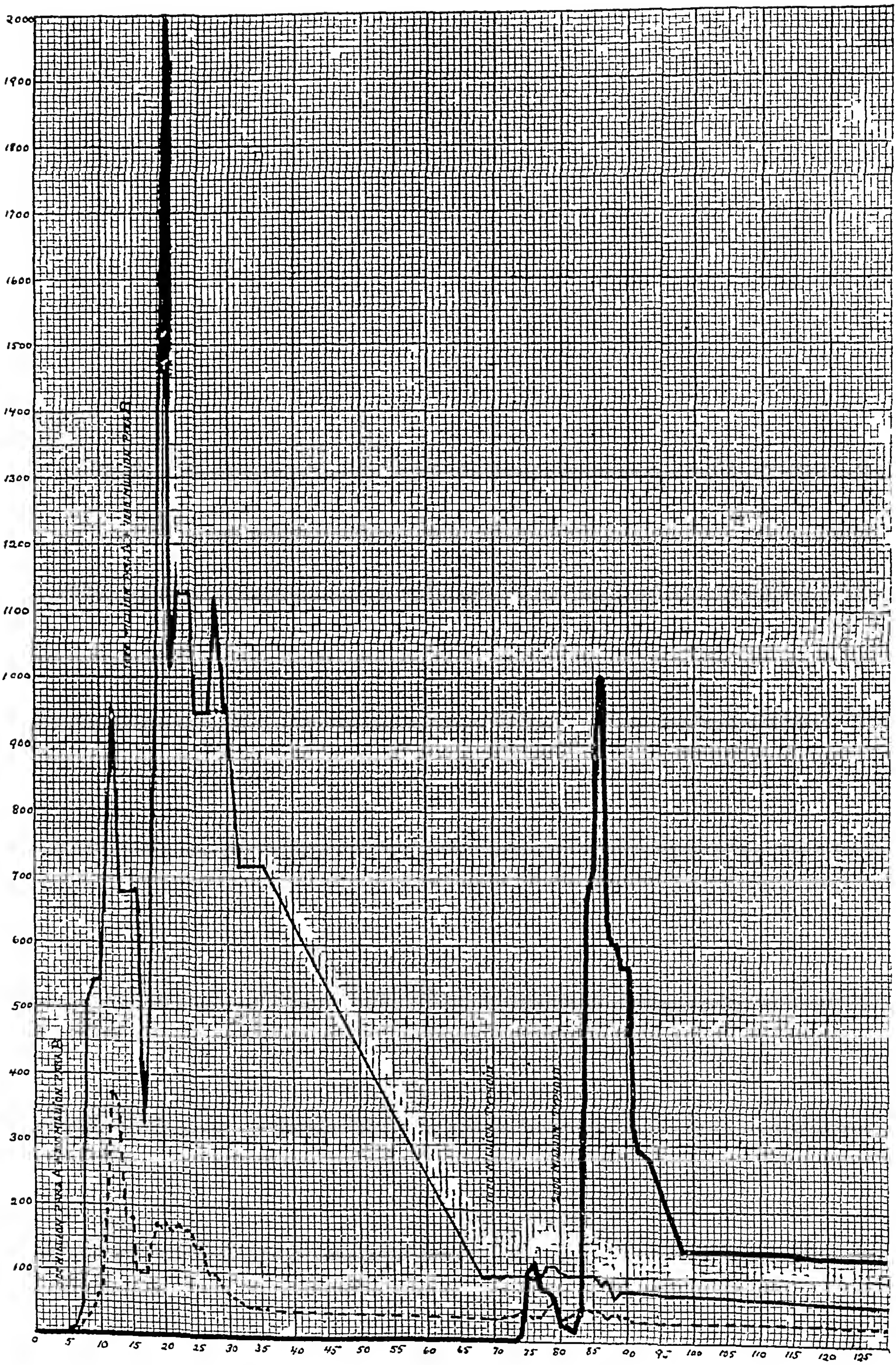
The paratyphoid A agglutinins commence their rise on the third day, reaching the maximum on the seventh A rapid fall then follows for four days The curve then shows no change for four The second inoculation was given at this point (fifteenth day) *A negative phase* occurs on the following day On the second day from this inoculation the curve quickly arises to a maximum (800 per cent) on the fifth day (twentieth from first inoculation) The curve shows no change when examined on the next day A rapid fall follows for the next two days No further examinations were made

The paratyphoid B curve commences on the fourth day after inoculation, reaching its maximum on the seventh day The titer gradually falls for the next eight days The second inoculation is given on the fifteenth day The B titer shows no change on the next day A small negative phase appears on the second day The titer then rises to its maximum on the fourth day (nineteenth day from the first inoculation), shows no change for three days, and then rapidly falls for two days No further examination was made

Rabbit 3—(Group 2, Curve 3) *The T agglutinins* are unaffected by the two doses of *A B* vaccine injected and the *T* titer did not rise above the base line On the fourth day after the first *T* inoculation (fifty-ninth day after the second *A B* inoculation, seventieth day after the first *A B* inoculation) the *T* titer rose, reaching a maximum on the sixth day It then fell for the next five days At this point the second *T* inoculation was given The titer showed no change the following day A negative phase was seen on the second day The curve began its new rise on the third day, reaching the maximum on the sixth day The titer then falls for the next twelve days after which it appears to have reached its point of equilibrium

The paratyphoid A curve commences its rise on the second day after inoculation, reaching its maximum on the eighth day On the ninth day the titer falls rapidly (33 per cent) and then shows no change until the eleventh day At this point the second inoculation was given The titer showed no change the following day A negative phase (50 per cent) appeared on the second day On the third day the titer rises, reaching its maximum (700 per cent) on the fifth day (from the second inoculation) The titer then falls rapidly (50 per cent) and shows no change for ten days, and then falls gradually until the thirty-second day from the first inoculation When examined after an interval of thirty-two days the titer has fallen 85 per cent The first *T* inoculation is given two days later A slight negative phase appears on the day following A slight rapid rise then ensues on the second day From this point the titer shows no change until the fifth day, when a fall commences, which continues until eighth day On the eighth day the *A* titer rises This corresponds with the maximum of the first rise in the *T* curve On the tenth day the second *T* inoculation is given This appears to have no appreciable effect on the *A* curve On the eighth day after the second *T* inoculation there is a fall in titer (40 per cent) after which the curve appears to have reached its equilibrium

The paratyphoid B curve rises on the third day after inoculation, reaching its maximum on the eighth day It then falls (10 per cent) and shows no change until eleventh day At this point the second inoculation is given A negative phase (45 per cent) is seen for the following two days The second rise commences on the third day after the second inoculation, reaching its maximum on the fourth where it appears to remain for the next three days, after which it gradually falls (66 per cent) until the twenty-first day (after the second *A B* inoculation) An interesting fact in the *B* Curves of both 2 and 3 is that the rise after the second *A B* inoculation is appreciably less



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Curve 3

TABLE 6—DATA FROM WHICH CURVE 3 WAS PLOTTED

Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	B paratyphosus A	B paratyphosus B
1	2,670	0	0	0
2	2,600	0	0	0
4	2,640	0	0	0
4	2,640	Inoculation, 1 c c A B = 500 million para A + 500 million para B		
5	2,420	0	0	0
6	2,440	0	2 25	0
7	2,450	0	45 04	3 08
8	2,420	0	508 47	26 45
9	2,424	0	540 54	46 29
10	2,370	0	540 54	77 15
11	2,350	0	675 68	185 18
12	2,330	0	945 94	370 37
13	2,430	0	675 68	343 95
14	2,350	0	675 68	180 0
15	2,250	0	675 68	180 0
15	2,250	Inoculation, 1 c c A B = 1,000 million para A + 1,000 million para B		
16	2,210	0	675 68	96 0
17	2,350	0	337 83	96 0
18	2,350	0	675 68	137 8
19	2,200	0	1,013 51	169 0
20	2,400	0	2,027 02	169 0
21	2,320	0	1,013 51	160 0
22	2,360	0	1,126 12	169 0
23	2,410	0	1,126 12	160 0
24	2,330	0	1,126 12	160 0
25	2,320	0	945 94	137 0
26	2,310	0	945 94	137 0
27	2,300	0	945 94	96 0
28	2,270	0	1,122 41	96 0
29	2,380	0	1,020 37	75 0
30	2,470	0	952 38	67 5
31	2,310	0	952 38	60 0
32	2,300	0	714 28	55 0
83	2,350	0	714 28	48 0
86	2,320	0	714 28	48 0
68	2,710	0	95 0	32 0
69	2,720	0	95 23	32 64
70	2,540	0	100 0	32 64

TABLE 6—DATA FROM WHICH CURVE 3 WAS PLOTTED—(*Continued*)

Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	*B paratyphosus A*	*B paratyphosus B*
70	2,540	Inoculation,	1 0 c c. = 1,000 million	T
71	2,570	0	95 23	32 64
72	2,560	0	100 0	35 71
73	2,430	0	100 0	35 71
74	2,500	3 15	100 0	44 64
75	2,500	120 0 – 246 0	99 11	44 64
76	2,510	126 0	95 23	35 71
77	2,660	79 0	95 23	35 71
78	2,580	79 0	112 24	53 57
79	2,420	67 0	112 24	56 11
80	2,480	32 2	107 14	35 71
80	2,480	Inoculation,	2 c c T = 2,000 millio	n T
81	2,500	32 2	100 0	35 71
82	2,490	29 0	100 0	50 0
83	2,480	59 5	100 0	50 0
84	2,500	670 0	100 0	50 0
85	2,520	720 0	100 0	50 0
86	2,420	1,000 0	88 59	50 0
87	2,335	630 0	99 11	35 71
88	2,410	600 0	62 50	44 64
89	2,500	561 0	71 42	32 14
90	2,380	561 0	71 42	32 64
91	2,680	590 0 – 322 0	59 52	30 35
92	2,510	290 0	64 28	30 35
93	2,500	280 0	64 28	30 35
94	2,220	255 0	56 11	30 35
96	2,500	280 0	64 28	30 35
98	2,630	137 98	54 0	30 35
100	2,600	137 98	54 0	30 35
102	2,900	137 98	59 0	30 35
104	2,720	137 98	59 0	30 35
106	2,720	137 98	82 7	30 35
108	2,720	137 98	51 5	30 35
112	2,760	137 98	59 0	30 35
116	2,740	137 98	42 0	30 35
120	2,980	130 0	42 0	30 35
125	2,880	130 0	51 5	25 5

TABLE 6—DATA FROM WHICH CURVE 3 WAS PLOTTED—(*Continued*)

Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	B paratyphosus A	B paratyphosus B
132	2,980	59 6	45 6	13 0
139	2,990	59 6	45 6	20 5
146		54 0	28 6	9 5
153		130 0	47 5	20 5
160		138 0	47 5	23 6
167		130 0	47 5	13 0

than the rise after the first inoculation, and unless one can suppose that a rapid rise and fall have occurred within twenty-four hours so that daily readings would not record it, it would appear that this forms an exception to the more general rule that the rise of agglutinins following the second inoculation is greater than that following the first

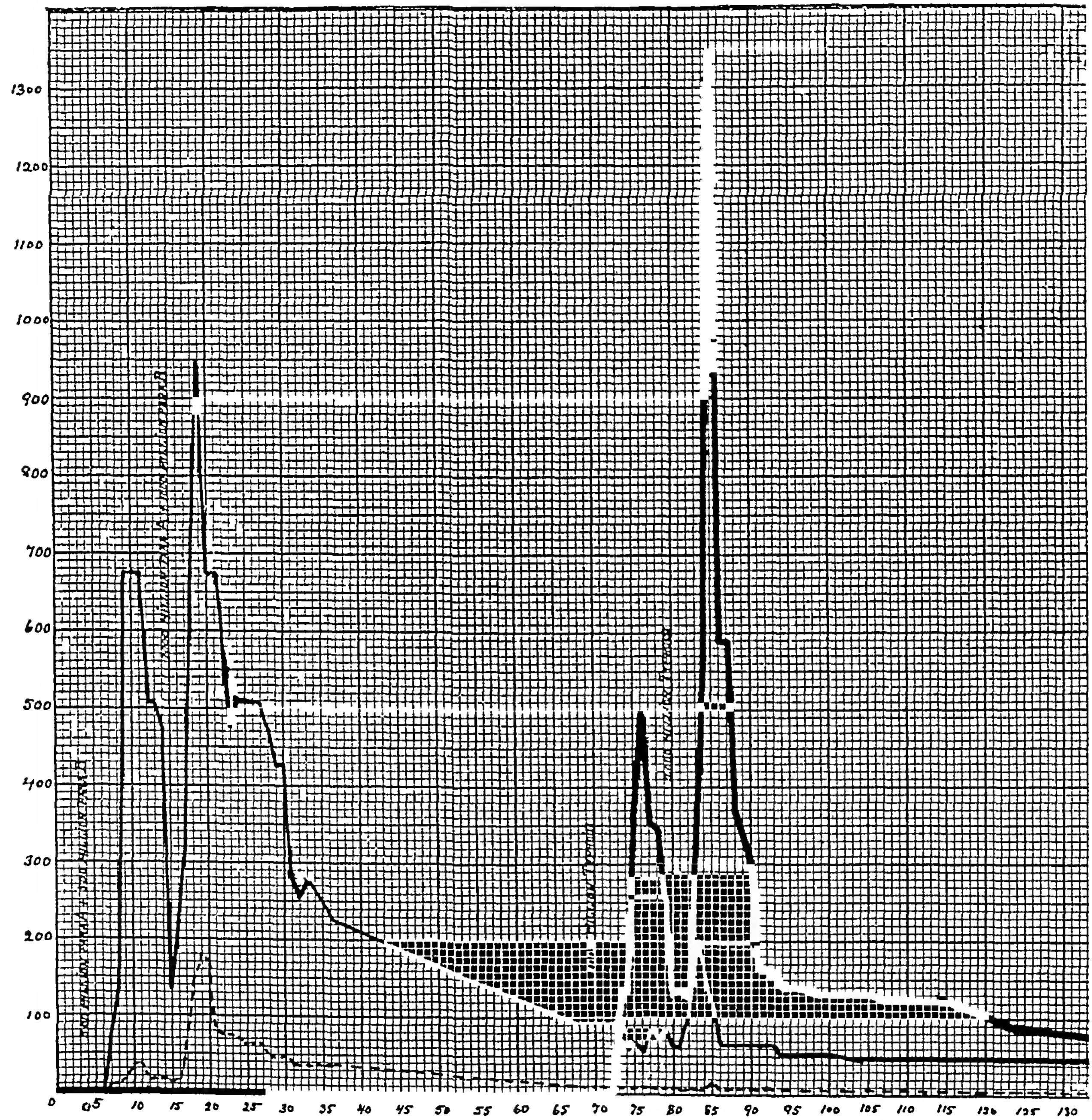
When next examined after an interval of thirty-two days the *B* titer has fallen 30 per cent The *T* inoculation is given on the sixty-sixth day (after the first inoculation) No appreciable negative phase occurs The rise of the *B* titer commences on the second day, reaching a maximum on the ninth, falling again on the tenth At this point the second *T* inoculation is given No negative phase occurs A rise to a maximum is noticed on the second day The curve then shows no further change until the fifth day, when it falls again, resuming its equilibrium on the ninth day (from the second typhoid inoculation, eighty-fifth day from first inoculation) The subsequent fall is very gradual

RABBIT 4—(Group 2, Curve 4) *The typhoid agglutinins* were unaffected by the two doses of mixed *A* and *B* vaccine injected and the typhoid titer did not rise above the base line On the third day after the first *T* inoculation (sixty-ninth day after the first *A B* inoculation, fifty-eighth day after the last *A B* inoculation), the *T* titer commenced to rise rapidly, reaching its maximum on the sixth day A rapid fall then follows until the tenth day At this point the second typhoid inoculation was given The curve shows no change for the first day, but a negative phase appears on the second day On the third day the rapid rise then commences, reaching its maximum (900 per cent) on the fifth day A rapid fall (30 per cent) followed by a more gradual one then ensues and by the eleventh day after the last *T* inoculation (eighty-seventh from the first *A B* inoculation) the *T* titer had reached its point of equilibrium

The paratyphoid A agglutinins commence their rise on the third day after inoculation, reaching their maximum on the fifth day The titer shows no change for three days A rapid fall (80 per cent) then follows, until the eleventh day At this point the second inoculation is given No negative phase is seen and the titer rises on the first day, reaching its maximum (700 per cent) on the fourth day (the fifteenth day after the first inoculation) The titer then falls rapidly (45 per cent) for the next four days and then shows no change for another four days, after which the fall is again rapid (25 per cent) until the twenty-first day after the second inoculation (thirty-second after the first)

When next examined after an interval of thirty-two days, the titer has dropped another 54 per cent and is practically in equilibrium The first *T* inoculation two days later (that is, fifty-five days after second *A B* inoculation and sixty-sixth day after first *A B* inoculation), causes the titer to rise on

the following day (no negative phase being seen), and a maximum is reached on the second day The titer regains its point of equilibrium on the tenth day At this point the second typhoid inoculation is given The titer then rises on the second day (no negative phase appearing), and a maximum is reached on the third day The succeeding fall is rapid and equilibrium is reached on the sixth day (eighty-second day after first *A B* inoculation) The subsequent fall in titer was but slight



Curve 4

The paratyphoid B agglutinins commence their rise on the third day after the first inoculation, reaching their maximum on the sixth day The titer shows very little change until the tenth day and falls slightly on the eleventh At this point the second inoculation is given The titer rises on the following day (no negative phase being seen) The maximum (300 per cent) is reached

TABLE 7—DATA FROM WHICH CURVE 4 WAS PLOTTED

Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	B paratyphosus A	B paratyphosus B
1		0	0	0
2	1 420	0	0	0
4	1 480	0	0	0
4	1,480	Inoculation,	1 c c A B = {500 million para A, 500 million para B}	
5	1,520	0	0	0
6	1,530	0	0	0
7	1,540	0	67 56	3 08
8	1,560	0	135 13	7 40
9	1,557	0	675 67	18 51
10	1,510	0	675 68	37 03
11	1,490	0	675 68	37 03
12	1,580	0	472 07	18 0
13	1,510	0	506 75	18 0
14	1,450	0	472 97	18 0
15	1,510	0	135 13	13 0
15	1,510	Inoculation,	2 c c A B = {1,000 million para A, 1,000 million para B}	
16	1 550	0	236 48	14 0
17	1,550	0	337 83	64 0
18	1,560	0	675 68	145 0
19	1,500	0	945 94	180 0
20	1,540	0	675 68	170 0
21	1,560	0	675 68	80 0
22	1,530	0	506 75	72 0
23	1,560	0	472 97	72 0
24	1,520	0	563 06	69 0
25	1,550	0	506 75	62 0
26	1,580	0	506 75	64 0
27	1,590	0	506 75	62 0
28	1,550	0	472 97	48 0
29	1,700	0	428 57	48 0
30	1,720	0	428 57	48 0
31	1,640	0	285 71	36 0
32	1,620	0	250 0	38 0
33	1,610	0	271 42	38 0
36	1,590	0	228 57	38 0
68	1,510	0	95 23	7 14

TABLE 7—DATA FROM WHICH CURVE 4 WAS PLOTTED—(*Continued*)

Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	B paratyphosus A	B paratyphosus B
69	1,580	0	95 23	7 14
70	1,600	0	71 42	7 14
70	1,600	Inoculation,	1 c c T = 1,000 million	typhoid
71	1,510	0	95 23	7 14
72	1,520	0	95 23	7 14
73	1,510	100 0	71 42	7 14
74	1,560	138 0	59 52	7 14
75	1,590	352 0	64 28	2 85 - 7 14
76	1,569	500 0	57 14	5 71
77	1,620	352 0	85 71	6 28
78	1,610	340 0	71 42	6 28
79	1,570	255 0	85 71	6 28
80	1,640	133 0	59 52	5 17
80	1,640	Inoculation,	2 c c T = 2,000 million	T
81	1,530	133 0	59 52	2 85
82	1,450	126 0	59 52 - 107 14	5 30
83	1,440	320 0	59 52 - 142 84	5 30
84	1,470	561 0	196 42 59 52 - 96 93	5 30
85	1,420	1,340 0	119 04	10 71
86	1,410	590 0 – 340 0	64 28	5 71
87	1,490	590 0 – 340 0	64 28	2 57
88	1,480	590 0 – 567 0	53 57	2 85
89	1,500	297 0 – 516 0	64 28	2 57
90	1,460	297 0	64 28	2 37
91	1,620	160 0	71 42	4 57
92	1,560	160 0	64 28	4 57
93	1,540	160 0	64 28	5 71
94	1,590	140 0	53 57	5 42
96	1,580	140 0	47 14	5 0
98	1,610	137 98	46 5	5 0
100	1,680	137 98	46 5	5 71
102	1,870	137 98	49 0	4 27
104	1,770	137 98	44 2	4 0
106	1,780	137 98	44 2	4 0
108	1,740	129 0	44 2	3 96
112	1,780	125 7	35 6	4 37

TABLE 7—Data from which Curve 4 Was Plotted—(*Continued*)

Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	B paratyphosus A	B paratyphosus B
116	1,840	125 7	35 6	4 37
120	1,940	103 9	42 5	5 71
125	2,030	87 5	51 5	2 3
132	2,060	60 0	45 0	1 28
139	2,160	59 4	40 0	1 92
146		65 0	50 0	2 55
153		65 0	50 0	1 92
160		52 0	47 5	1 92
167		43 0	43 0	1 02

on the fourth day A rapid fall (56 per cent) follows until the seventh day From this point until the sixteenth day the fall is more gradual (25 per cent) There is but slight change in titer from the sixteenth to nineteenth day after the second inoculation (twenty-seventh to thirtieth day after the first inoculation) When examined again after an interval of thirty-two days (sixty-fourth day after the first *A B* inoculation) the titer dropped another 80 per cent and had reached a *point of equilibrium* The first *T inoculation* two days later (fifty-fifth day after the last *A B* inoculation, sixty-sixth day after the first *A B* inoculation) had no appreciable effect on the *B* titer The second *T* inoculation was given ten days later A negative phase occurred on the following day and the titer rose on the second day, reaching a maximum on the fifth day, falling again to its point of equilibrium on the seventh day

Rabbit 5—(Group 3, Curve 5) *The typhoid agglutinins* commenced their rise on the third day after inoculation, attaining their maximum on the eleventh day At this point the second *T* inoculation was given The titer showed no change for the next three days (no negative phase being seen) On the fourth day after the last inoculation (the fifteenth after the first) the titer rose rapidly, reaching its maximum (100 per cent) the same day The curve shows no change for the next two days and then rapidly falls (25 per cent) on the seventh and eighth days The titer shows no change for the next four days and then gradually falls another 25 per cent until the sixteenth day (twenty-seventh from the first inoculation) The titer from the sixteenth to twenty-first day shows no change When next examined after an interval of thirty-two days a further fall (37 per cent) has taken place and the curve has evidently reached its point of equilibrium The first inoculation of *A B* vaccine two days later (that is, fifty-fifth day from the last *T* inoculation and sixty-sixth from the first) has no effect on the *T* titer, but the second *A B* inoculation ten days later causes the titer to rise on the fifth day (no negative phase being seen) The maximum is reached on the eighth day On the eleventh day (eighty-eighth day after the first *T* inoculation) the curve has resumed its point of equilibrium and the subsequent fall is but gradual

The paratyphoid A agglutinins show a slight rise on the fifth day after the first *T* inoculation which reaches its maximum on the eleventh day At this point the second *T* inoculation is given The only effect produced on the *A* titer is that it does not show the natural fall, no change from the maximum produced by the first inoculation being noted until the nineteenth day after the last inoculation (that is thirtieth day after the first inoculation) When

TABLE 8—DATA FROM WHICH CURVE 5 WAS PLOTTED

Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	B paratyphosus A	B paratyphosus B
1	2,170	0	0	0
2	2,170	0	0	0
4	2,060	0	0	0
4	2,060	Inoculation,	1 c c T = 1,000 million	typhoid
5	2,000	0	0	0
6	2,060	1 59	0	0
7	2,140	21 27	0	0
8	2,140	197 53	0	0
9	2,120	354 59	0	1 18
10	2,060	443 25	0	0 78
11	2,060	417 87	0	0
12	2,080	319 14	0	0
13	2,140	443 25	1 01	0
14	2,070	478 72	1 01	0
15	2,230	531 91	2 7	0 78
15	2,230	Inoculation,	2 c c T = 2,000 million	typhoid
16	2,050	531 91	2 7	1 52
17	2,030	531 91	2 7	0 96
18	2,040	531 91	0	0 96
19	1,950	1,063 82	0	0 96
20	2,050	930 85	0	0 96
21	2,110	1,063 82	0	1 70
22	2,170	886 38	0	0 56
23	2,180	797 87	0	1 92
24	2,100	797 87	0	1 56
25	2,140	797 87	0	1 52
26	2,060	759 85	0	1 48
27	2,070	759 85	0	1 48
28	2,200	661 37	0	1 48
29	2,100	661 37	0	0 96
30	2,220	566 89	0	0
31	2,130	529 1	0	0
32	2,090	396 82	0	0
33	2,030	529 1	0	0
36	2,070	529 1	0	0
68	2,080	256 0	0	0
69	2 020	256 0	0	0
70	2,000	256 0	0	0

TABLE 8—DATA FROM WHICH CURVE 5 WAS PLOTTED—(*Continued*)

Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	B paratyphosus A	B paratyphosus B
70	2,000	Inoculation, 1 c c A B = 500 million A + 500 million B		
71	2,170	256 0	0	0
72	2,170	256 0	7 14	0
73	2,080	256 0	612 14	61 21
74	2,140	256 0	2,500 0	128 57
75	2,120	256 0	2,652 0	142 85
76	2,060	256 0	2,500 0	128 57
77	2,160	256 0	2,346 57	236 68
78	2,150	220 0	1,071 2	128 57
79	2,220	256 0	1,071 42	142 85
80	2,220	256 0	1,160 71 663 26	107 14
80	2,220	Inoculation, 2 c c A B = 1,000 million A + 1,000 million B		
81	2,270	256 0	969 38 - 561 14	107 14
82	2,270	256 0	595 23	107 14
83	2,280	256 0	714 28	142 85
84	2,210	256 0	2,040 57	714 28
85	2,300	280 0	2,625 29	1,190 4
86	2,320	305 0	2,500 0	1,000 0
87	2,280	280 0	3,142 85	1,000 0
88	2,320	320 0	2,500 0	714 28
89	2,220	305 0	2,500 0	595 23
90	2,210	280 0	2,500 0	595 23
91	2,410	256 0	2,142 85	500 0
92	2,280	256 0	2,142 85	535 71
93	2,240	256 0	2,142 85	500 0
94	2,520	256 0	1,285 71	500 0
96	2,280	256 0	2,142 85	446 42
98	2,410	243 5	982 0	303 57
100	2,350	243 5	982 0	303 57
102	2,450	433 0	1,090 0	326 0
104	2,380	271 0	885 0	326 0
106	2,370	282 0	885 0	326 0
108	2,350	271 0	885 0	326 0
112	2 330	243 5	825 0	326 0
116	2,880	162 0	590 0	285 0
120	2,600	148 0	530 0	228 0
125	2,620	148 0	522 0	228 0
132	2,510	121 0	285 0	64 8

TABLE 8.—DATA FROM WHICH CURVE 5 WAS PLOTTED. (Continued)

The *A* and *B* agglutinins were unaffected by the injections of *T* vaccine and their titer did not rise above the base line here

[illegible]	2,010	[illegible]	[illegible]	[illegible]

TABLE 8—Data from which Curve 5 Was Plotted—(*Continued*)

Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	B paratyphosus A	B paratyphosus B
139	2,580	243 0	530 0	236 0
146		148 5	450 0	64 0
153		138 0	430 0	64 0
160		114 0	400 0	64 0
167	•	104 0	400 0	59 2

next examined after an interval of thirty-two days the titer has regained the base line of normal agglutination The first *A B* inoculation is given two days later, that is, on the fifty-third day after the last *T* inoculation (sixty-sixth day after first *T* inoculation) The *A* curve commences its rise on the second day, reaching its maximum on the fifth day The titer then shows no change for the next two days A rapid fall (72 per cent) ensues from the third to tenth day At this point the second *A B* inoculation is given A negative phase (6 per cent) is seen for the next two days and the rise of titer commences on the third day, reaching its maximum (475 per cent) on the seventh day after the last inoculation The titer then falls 16 per cent on the next day and then shows no change for the next three days By the eleventh day a rapid fall (31 per cent) occurs From this point the curve is evidently in equilibrium, as the fall is but gradual

The paratyphoid B agglutinins commence their small rise four days after the first *T* inoculation, reaching their maximum on the next day (fifth) A small fall (33 per cent) occurs on the sixth day From this point until the eleventh day the titer appears to remain a small distance above the base line of normal agglutination The second inoculation is given on the eleventh day and the titer commences to rise on the following day (no negative phase being seen), and reaches its maximum (150 per cent) on the eighth day The titer then falls gradually until the fourteenth day (from second *T* inoculation, twenty-fifth day from the first inoculation) From this point until the twenty-seventh day (after the last inoculation) and after an interval of thirty-two days the titer had not risen above the base line of normal agglutination The first *A B* inoculation is given two days later (that is, fifty-fifth day after the last *T* inoculation and sixty-sixth day after the first) The *B* agglutinins commence their rise on the third day following, reaching the maximum on the fourth day A sharp fall (40 per cent) is shown the next day, after which a more gradual fall (a further 14 per cent) takes place until the tenth day At this point the second *A B* inoculation is given The titer rises on the third day, reaching a maximum (1,000 per cent) on the fifth day A rapid fall (60 per cent) follows from the fifth to eleventh day From this point the curve shows no change for four days, and then falls until the sixteenth day From this point until the eighty-seventh day (after the last inoculation) the fall is but gradual

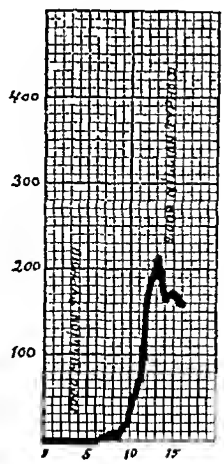
Rabbit 6—(Group 3, Curve 6) The typhoid agglutinins commenced their rise on the third day after the first inoculation, reaching the maximum on the ninth day The titer fell (20 per cent) on the tenth day and shows no change on the eleventh day The second inoculation was given at this point A negative phase occurred on the next day

The death of Rabbit 6 from a broken neck, due to fighting with another rabbit in the same cage, brought an end to the experiment at this point

The *A* and *B* agglutinins were unaffected by the injections of *T* vaccine and their titer did not rise above the base line here

TABLE 9—DATA FROM WHICH CURVE 6 WAS PLOTTED

Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	B paratyphosus A	B paratyphosus B
1	1,280	0	0	0
2	1,240	0	0	0
4	1,250	0	0	0
4	1,250	Inoculation,	1 c c T = 1,000 million	typhoid
5	1,250	0	0	0
6	1,300	0	0	0
7	1,350	1 41	0	0
8	1,410	3 19	0	0
9	1,440	8 86	0	0
10	1,360	26 59	0	0
11	1,350	70 91	0	0
12	1,580	159 59	0	0
13	1,350	212 76	0	0
14	1,260	159 57	0	0
15	1,400	170 21	0	0
15	1,400	Inoculation,	2 c c T = 2,000 million	typhoid
16	1,310	159 57	0	0



Curve 6

RABBIT 7—(Group 7, Curve 7) *The typhoid agglutinins* commenced their rise on the third day after the first triple inoculation The titer then rose rapidly until the ninth day, when the second inoculation was given The curve continues its rapid rise to an apex on the twelfth day after the first triple inoculations (third day after the second triple inoculation) No negative phase, nor any break in the continuity of the curve (that is, no fall or plateau) was seen, until the fourth day (after the second inoculation) when a fall of 11 per cent was noted

TABLE 10—DATA FROM WHICH CURVE 7 WAS PLOTTED

Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	B paratyphosus A	B paratyphosus B
1	1,360	0	0	0
2	1 290	0	0	0
2	1,290	Inoculation,	1 c c T A B = 1,000 million T, 500 million A, 500 million B	
3	1,270	0	0	0
4	1,320	0	2 2	0
5	1,330	14 4	35 71	5 7
6	1,320	64 5	119 04	21 42
7	1,300	240 0	357 14	71 42
8	1,420	340 0	595 23	85 71
9	1,410	340 0	561 14	71 42
10	1,400	562 0	491 7	98 21
11	1,400	620 0	357 14	112 24
11	1,400	Inoculation,	2 c c T A B = 2,000 million T, 2,000 million A, 1,000 million B	
12	1,330	805 0	564 28	119 04
13	1,440	1,260 0	948 85	236 68
14	1,390	1,405 0	1,160 71	236 68
15	1,370	1,260 0	2,500 0	357 14
16	1,420	1,305 0	2,652 57	595 23
17	1,390	1,470 0	4,910 71	642 85
18	1,350	2,982 0	5,611 42	627 14
19	1,410	2,982 0	5,611 42	969 3 – 627 14
20	1,470	2,982 0	23,465 71	642 85
21	1,360	3,672 63	14,285 71	1,142 85 - 1,285 71
22	1,460	3,672 0	12 500 0	2,500 0
23	1,430	3,672 0	30,357 14	1,309 51
24	1,410	7,031 25	211,428 57 71,428 57 214,285 71	
25	1,450	5,625 0	13,264 57	2,597 40
27	1,470	2,711 04	10,949 0	2,366 85
29	1,530	2,705 58	10,318 0	2,366 85
31	1,510	2,029 22	23,584 0	2,232 14
33	1,650	1,483 89	10,318 0	1,326 45
35	1,560	1,623 37	20,636 0	2,232 14
37	1,570	1,379 87	11,792 0	2,232 14
39	1,590	1,379 87	11,792 0	2,232 14
43	1,630	1,205 71	15,896 0	2,105 26
47	1,730	1,066 62	4,913 0	714 28
51	1,830	892 0	4,632 0	1,122 0

TABLE 10—DATA FROM WHICH CURVE 7 WAS PLOTTED—(*Continued*)

Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	B paratyphosus A	B paratyphosus B
56	1,890	603 0	4,350 0	850 0
63	1,910	578 0	4,750 0	520 0
70	1,900	541 0	4,190 0	466 0
77		520 0	4,500 0	477 0
84		405 0	3,900 0	280 0
91		520 0	4,500 0	291 0
98		405 0	3,440 0	280 0

On the fifth day (after the second inoculation) the titer resumes its rise, reaching a maximum on the thirteenth day The titer then falls rapidly (70 per cent) from this point until the forty-fourth day The *T* titer is then evidently in equilibrium for the fall from this point is but gradual

The apex and subsequent fall of the curve noted, respectively, on the twelfth and thirteenth days after the first inoculation (third and fourth days after the second) might well represent the maximum of the rise due to the first inoculation and the negative phase following the second inoculation, even though this apex occurs after the second inoculation For, as I shall point out later in the men's curves, if the second inoculation is given before the maximum of the rise due to the first inoculation is attained, a continuation of this rise to an apex and a subsequent fall may occur after the second inoculation, which suggests the maximum of the rise due to the first inoculation and the negative phase following the second inoculation After this fall the titer resumes its rise, and the maximum due to the second inoculation is attained later As the inoculations were given at a shorter interval (that is, nine days) in this experiment than in the others in the rabbits, it may explain this rise and fall which precedes the maximum of the second inoculation

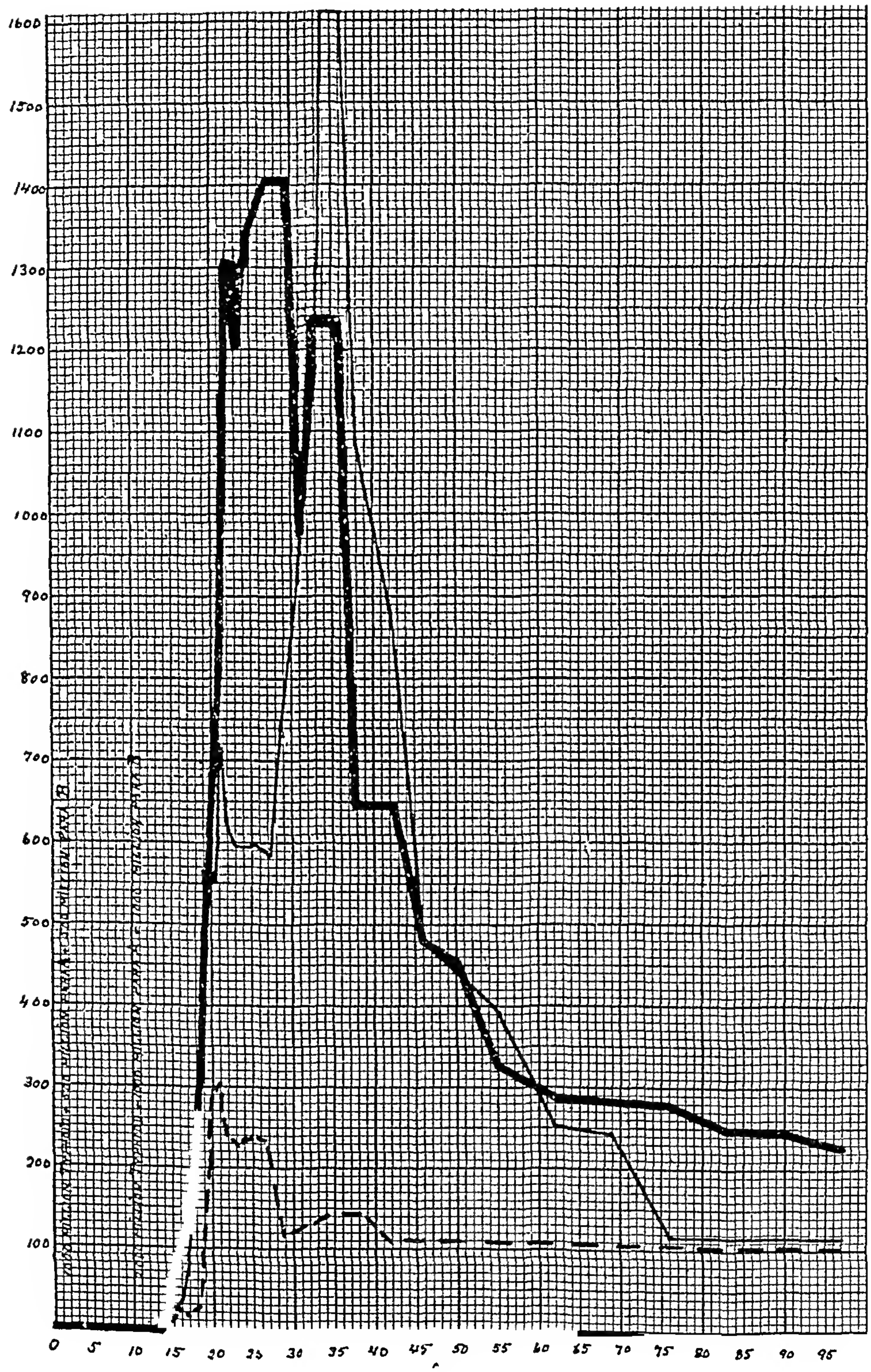
The paratyphoid A agglutinins commenced their rise on the second day after the first inoculation, reaching their maximum on the sixth day A rapid fall (40 per cent) then takes place until the ninth day At this point the second inoculation takes place and the titer rises rapidly on the next day (no negative phase being seen)

The maximum of this second rise occurs on the ninth day (650 per cent) or the twelfth day (750 per cent) after the second inoculation

The titer then falls until the thirty-sixth day (after the second inoculation) From this point the fall is but gradual and the curve appears to be in equilibrium

The paratyphoid B agglutinins commence their rise in the third day The titer then rises until the ninth day At this point the second inoculation is given and the titer continues its rise (no negative phase being seen) and the maximum is reached on the thirteenth after the second inoculation A rapid fall of titer (25 per cent) then takes place on the fourteenth to twenty-first day after the second inoculation From this point the titer shows no change for the next eight days and then another rapid fall (another 50 per cent) occurs until the thirty-sixth day At this point the curve appears to have reached its point of equilibrium for the subsequent fall is but gradual

RABBIT 8—(Group 4, Curve 8) As the first inoculation produced absolutely no rise in agglutinative titer, the curves can best be interpreted by assuming that the first dose instead of being injected into the peritoneal cavity was, as is known to happen occasionally, injected directly into the bowel and the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Curve 8

TABLE 11—DATA FROM WHICH CURVE 8 WAS PLOTTED

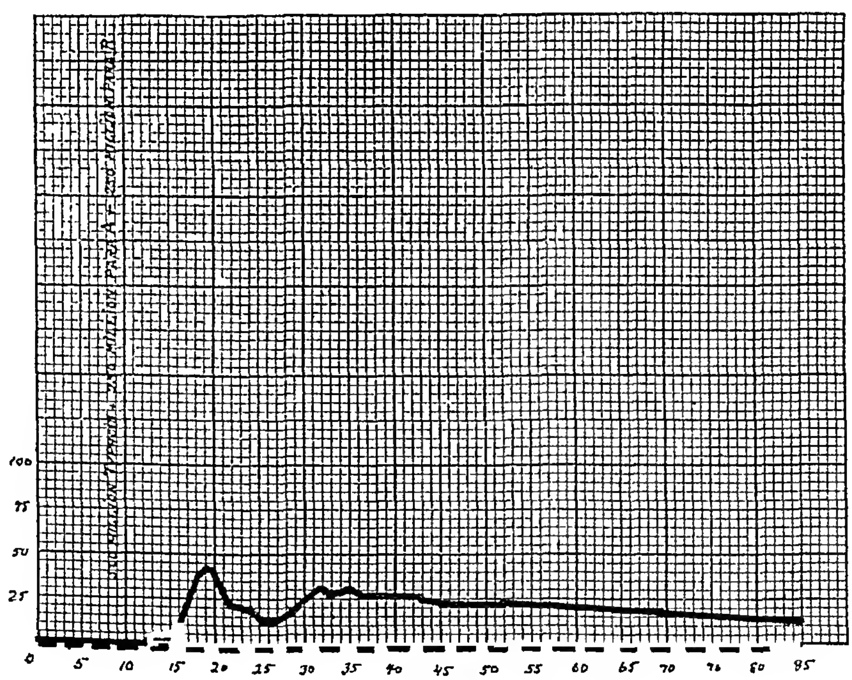
Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	B paratyphosus A	B paratyphosus B
1	1,290	0	0	0
2	1,210	0	0	0
2	1,210	Inoculation,	1 c c T A B = {1,000 million T, 500 million A, 500 million B}	
3	1,280	0	0	0
4	1,260	0	0	0
5	1,240	0	0	0
6	1,310	0	0	0
7	1,250	0	0	0
8	1,300	0	0	0
9	1,250	0	0	0
10	1,260	0	0	0
11	1,270	0	0	0
11	1,270	Inoculation,	2 c c T A B = {2,000 million T, 1,000 million A, 1,000 million B}	
12	1,220	0	0	0
13	1,300	0	0	0
14	1,350	11 9	4 76	2 85
15	1,350	56 25	22 44	14 28
16	1,270	100 0	32 64	23 66
17	1,320	126 0	85 71	11 90
18	1,210	220 0	234 65	28 57
19	1,260	400 0	561 14	125 0
20	1,360	630 0	551 94	285 71
21	1,300	805 0	714 28	303 57
22	1,390	1,306 0	625 0	236 68
23	1,350	1,200 0	595 23	228 57
24	1,380	1,306 0	595 23	236 68
25	1,450	1,340 0	595 23	236 68
27	1,420	1,400 0	586 73	236 68
29	1,450	1,405 0	739 0	119 04
31	1,490	974 02	960 0	125 0
33	1,630	1,233 76	1,180 0	132 64
35	1,570	1,233 76	1,610 0	142 85
37	1,570	1,233 76	1,610 0	142 85
39	1,520	649 35	1 082 0	142 85
43	1,480	649 35	885 0	107 14
47	1,570	482 35	490 0	107 14
51	1 720	455 0	442 0	119 0
56	1,580	325 0	400 0	57 0

TABLE 11—Data from which Curve 8 Was Plotted—(*Continued*)

Day of Experiment	Weight of Rabbit, Gm	Standard Agglutinin Units		
		B typhosus	B paratyphosus A	B paratyphosus B
63	1,260	284 0	251 0	106 0
70	1,828	325 0	243 0	119 0
77		270 0	114 0	111 0
84		243 0	114 0	111 0
91		243 0	114 0	115 0
98		227 0	114 0	128 0

vaccine voided without any absorption Therefore it is within the range of probability that Curve 8 should be regarded as the result of a single inoculation, that is, 2 c c containing 2,000 million T and 1,000 million A and 1,000 million B

The typhoid agglutinins are unaffected by the first inoculation (inoculating needle probably punctured the bowel and the vaccine was voided) but commence their rise on the third day after the second inoculation and reach the maximum on the eighteenth day after this inoculation At this point the titer shows no change for the next two days and then falls rapidly (65 per cent) until the thirty-sixth day when it appears to have reached its point of equilibrium for the subsequent fall is but gradual



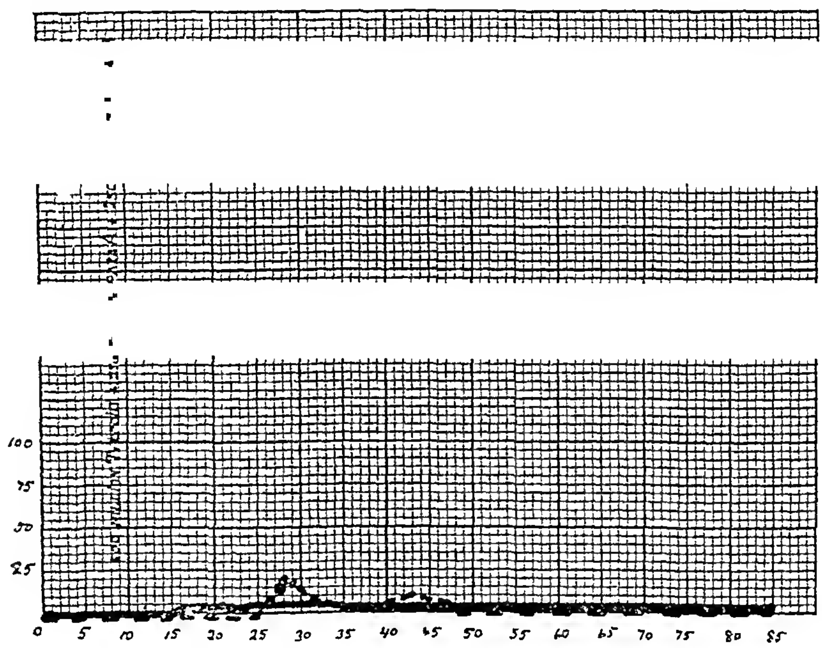
Curve 9

The paratyphoid A agglutinins are not affected by the first inoculation (which was probably voided unabsorbed), but commence their rise on the third day after the second inoculation The maximum is reached on the tenth day after the second inoculation The titer then falls rapidly (17 per cent) until the twelfth day At this point the titer shows no change until the sixteenth day From this point until the twenty-fourth day a further rise in titer is noted

(270 per cent) This latter rise is anomalous and somewhat difficult of explanation From this point until the thirty-sixth day a fall (69 per cent) occurs At this point the curve appears to have reached equilibrium, for the subsequent fall is but gradual

The paratyphoid B agglutinins are unaffected by the first inoculation (which was probably voided unabsorbed) but commence their rise on the third day after the second inoculation The maximum of this rise is reached on the tenth day From this point the curve falls and then shows no change until the eighteenth day when a fall (50 per cent) occurs From this point the curve appears to be in equilibrium, for with the exception of a few small fluctuations the subsequent fall is but gradual

Rabbit 9—(Group 5, Curve 9) *The typhoid agglutinins* showed a slight rise on the fourth day after this inoculation which reached its maximum on the tenth day The curve shows no further change for the next two days It then falls, reaching its point of equilibrium on the twenty-eighth day, for from this point until the seventy-seventh day the fall was but gradual



Curve 10

The paratyphoid A agglutinins show a slight rise on the second day after this inoculation The titer shows no change for the next three days and then falls, reaching the base line of normal agglutination by the seventh day

The paratyphoid B agglutinins show no rise above the base line of normal agglutination

Rabbit 10—(Group 5, Curve 10) *The typhoid agglutinins* did not show a rise until the seventh day after the inoculation From this point they rose to a maximum on the twelfth day The titer fell on the next two days and then regained its former height and showed no further change until the twenty-fourth day From the twenty-fourth to thirty-fourth day the titer fell 58 per cent This was the point of equilibrium for from this point to the seventy-seventh day the fall was but gradual

The paratyphoid A agglutinins did not rise above the base line of normal agglutination

TABLE 12—Data from which Curve 9 Was Plotted

Day of Experiment	Standard Agglutinin Units		
	B Typhosus	B Paratyphosus A	B Paratyphosus B
1	0	0	0
2	0	0	0
3	0	0	0
5	0	0	0
9	Inoculated 0 5 c c T A B = 500 million T + 250 million A + 250 million B		
10	0	0	0
11	0	1 38	0
12	0	1 38	0
13	2 5	1 38	0
14	3 5	0 69	0
15	5 0	0 69	0
16	8 41	0 69	0
17	25 0	0 69	0
18	39 4	0	0
19	41 6	0	0
20	41 6	0	0
21	31 2	0	0
22	21 8	0	0
23	21 8	0	0
24	18 7	0	0
25	12 5	0	0
26	12 5	0	0
29	17 7	0	0
32	31 2	0	0
33	25 0	0	0
35	31 25	0	0
37	25 0	0	0
39	25 0	0	0
41	25 0	0	0
43	25 0	0	0
46	21 8	0	0
48	21 8	0	0
50	21 8	0	0
52	21 8	0	0
56	13 8	0	0

TABLE 13—DATA FROM WHICH CURVE 10 WAS PLOTTED

Day of Experiment	Standard Agglutinin Units		
	B Typhosus	B Paratyphosus A	B Paratyphosus B
1	0	0	0
2	0	0	0
3	0	0	0
5	0	0	0
9	0	0	0
9	Inoculated 0 5 c c T A	B = 500 million T + 250 mi	llion A + 250 million B
10	0	0	0
11	0	0	0
12	0	0	0
13	0	0	0
14	0	0	0
15	0	0	0
16	0 62	0	0
17	1 8	0	0
18	1 8	0	0
19	0 62	0	0
20	1 2	0	0
21	4 38	0	0
22	2 5	0	0
23	2 5	0	0
24	4 38	0	0
25	4 38	0	0
26	4 38	0	3 7
29	4 38	0	18 5
32	4 38	0	2 78
33	4 33	0	1 85
35	3 7	0	0 0
37	0 0	0	0 0
39	2 07	0	3 7
41	0 0	0	0 0
43	1 8	0	9 25
46	1 8	3 2	7 4
48	0 0	0	3 7
50	1 8	0	3 7
52	1 66	0	1 85
86	0 79	0	0 0

The paratyphoid B agglutinins did not show a rise until the seventeenth day after the inoculation A maximum was reached the next day A fall then occurred until the twenty-eighth day On the thirtieth day to thirty-fourth day an increase in paratyphoid *B* titer is noticed From this point to the forty-third day a fall (80 per cent) takes place When examined on the seventy-seventh day there were no paratyphoid *B* agglutinins above the base line of normal agglutination

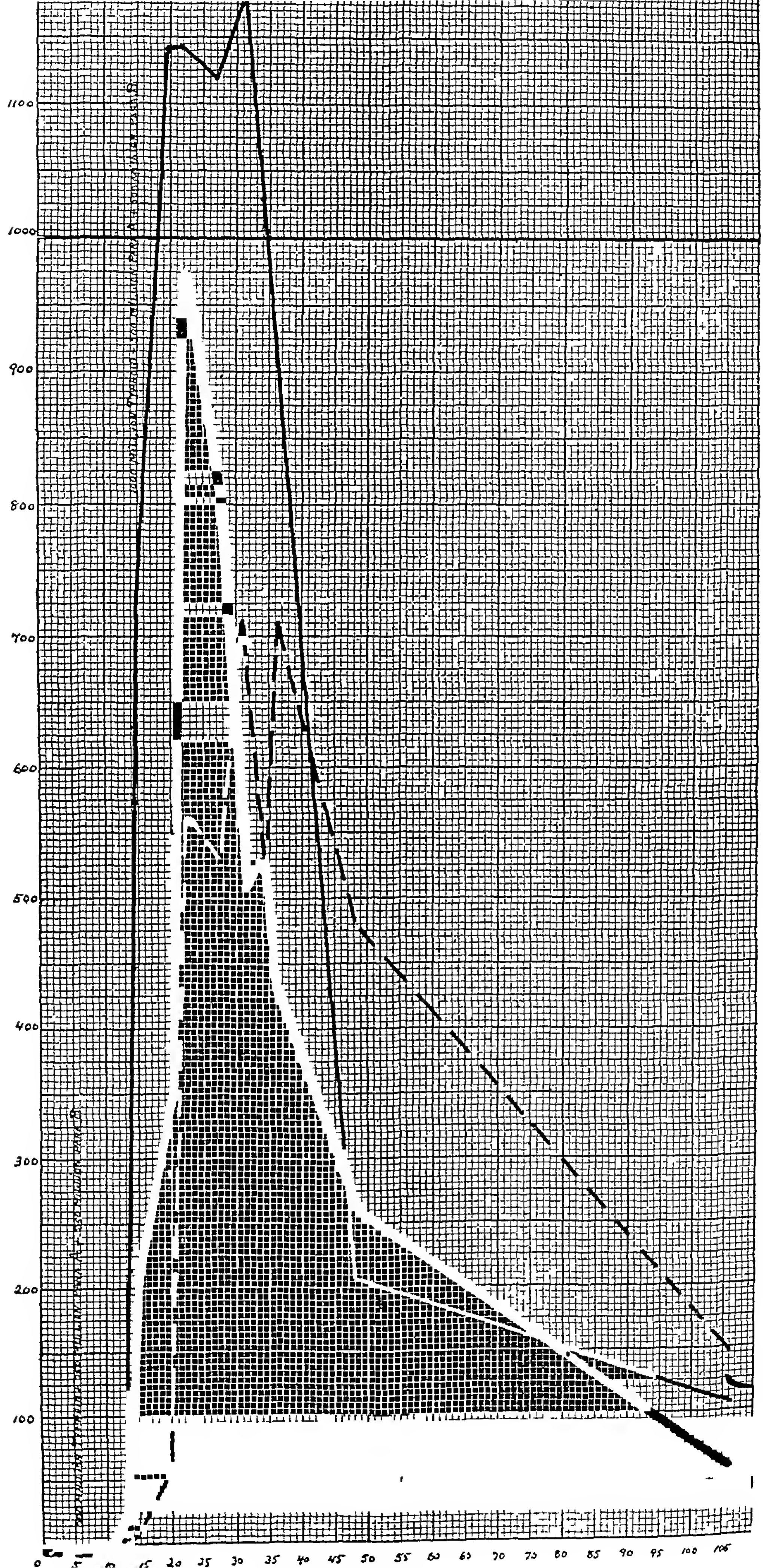
CURVES FROM MEN

None of the men in the following experiments presented any history of a previous infection with *B typhosus, B paratyphosus A* or *B paratyphosus B* The men of Groups VI to IX, inclusive, presented no history of a previous inoculation with any of these organisms The blood was always examined once before inoculation to determine the base line of normal agglutination The local and general reactions to each inoculation, even to the increased dosage in Curves 22 and 23, were in no way severe The individual on the day following each of the first and second inoculations usually developed a very mild headache, a feeling of "sleepiness" and a slight soreness at the point of inoculation, but this passed away the next day He was not prevented from going about his usual occupation In the case of the third and fourth inoculation, the local and general reactions were negligible

W G—(Group 6, Curve 11) *The typhoid agglutinins* had not commenced to rise on the fourth day but showed a rise on the seventh day following the first triple inoculation By the ninth day the titer had risen (85 per cent) At this point the second triple inoculation was given The curve had continued to rise when examined on the fifth day after this inoculation The *T* titer reaches its maximum on the seventh day after the second triple inoculation From this point to the thirty-fourth day the titer falls (74 per cent)

The paratyphoid A agglutinins had not commenced to rise on the fourth day but showed a rise on the seventh day after the first triple inoculation, which was increased by 2,400 per cent by the ninth day At this point the second triple inoculation was given The *A* titer continued to rise (70 per cent) by the fifth day The curve shows no change on the seventh day A slight fall is noted on the twelfth day On the sixteenth day a further rise is noted which may be taken as the maximum of the curve From this point to the thirty-fourth day the titer falls (81 per cent)

The paratyphoid B agglutinins had not commenced to rise on the fourth and seventh day but showed a rise on the ninth day after the first triple inoculation At this point the second triple inoculation is given The curve continued to rise when examined on the fifth and seventh day after the second triple inoculation On the twelfth day a slight fall in titer is noted, which, as it corresponds with the drop previously described on the same day in the *A* curve, may be of some significance By the sixteenth day the curve has risen again to a point which may be taken as its maximum On the nineteenth day a fall to a point equal to that of the twelfth day is noticed, to be followed on the twenty-first day by a rise equal in amount From this point to the thirty-fourth day the titer falls (25 per cent) The apparent irregularities in the maximum of this curve may be explained by saying that inasmuch as the irregularities of the paratyphoid curves correspond quite closely, they are due to an actual change in state of the individual It is also possible that the apex of the *A* titer on the fifth day (after the second inoculation) and the apex of the *B* titer on the seventh day, represent the maximum of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85
90
95
100
105

TABLE 14—Data from which Curve 11 Was Plotted

Day of Experiment	Standard Agglutinin Units		
	B Typhosus	B Paratyphosus A	B Paratyphosus B
1	0	0	0
6	Inoculation, 0 5 c c T A	B = 500 million T + 250 mi	llion A + 250 million B
10	0	0	0
13	24 1	29 0	0
15	Inoculation, 1 0 c c T A	B = 1,000 million T + 500	million A + 500 million B
15	210 0	710 0	5 06
20	344 0	1,142 0	56 0
22	970 0	1,142 0	561 0
27	805 0	1,122 0	532 0
31	510 0	1,180 0	712 0
34	530 0	1,030 0	532 0
36	432 0	927 0	712 0
48	263 0	206 0	476 0
106	56 5	106 0	146 0

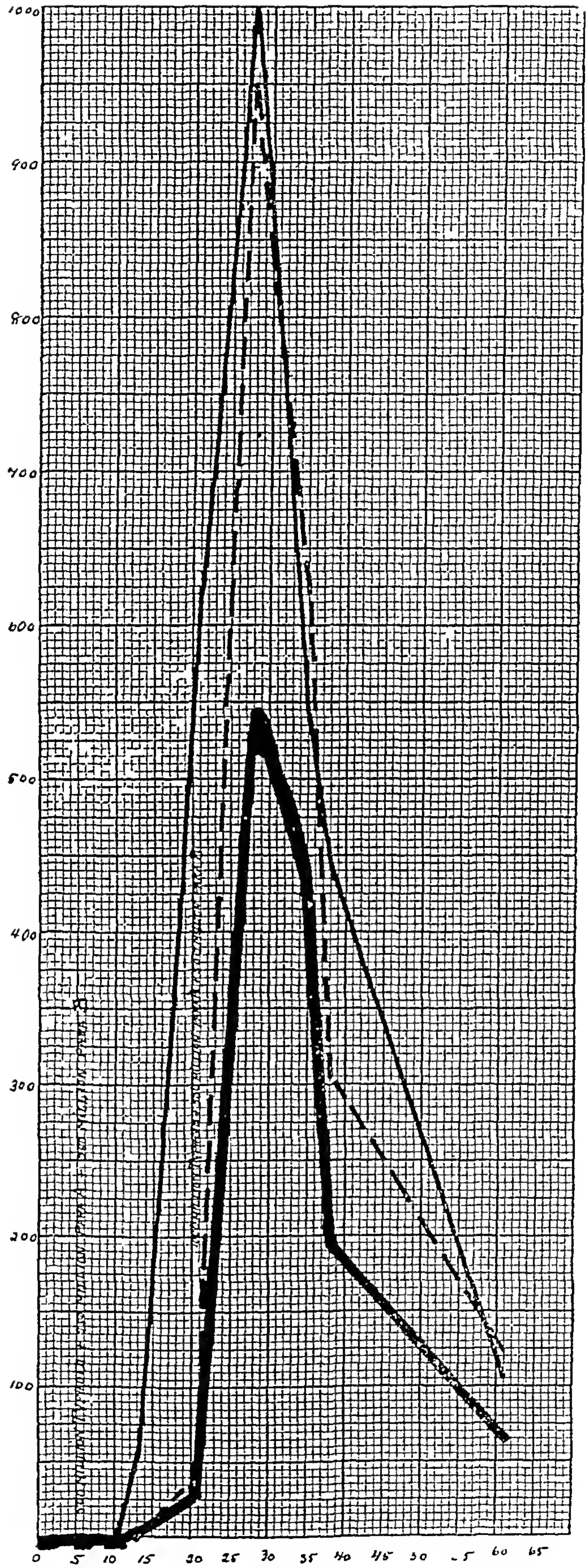
the rises due to the first inoculation. In that case the drop noted on the twelfth day may either be the normal fall in titer following a maximum, or a negative phase. The maximum noted on the sixteenth day would represent the maximum of the rise due to the second inoculation.[30]

J. G. J.—(Group 6, Curve 12.) *The typhoid agglutinins* had not commenced to rise on the fifth day after the first triple inoculation, but showed a slight rise on the seventh day which had greatly increased by the fifteenth day. At this point the second triple inoculation was given. The titer continued rising, reaching a maximum on the seventh day after the last inoculation. From the seventh to fortieth day (after the second triple inoculation) the *T* titer fell (88 per cent.)

The paratyphoid A agglutinins had not commenced to rise on the fourth day after the first triple inoculation, but showed a rise on the seventh day which was greatly increased by the fifteenth day. At this point the second triple inoculation was given. The *A* titer had reached a maximum when next examined on the seventh day after the second triple inoculation. From the seventh to fortieth day the *A* titer fell (89 per cent.)

The paratyphoid B agglutinins had not commenced to rise on the fourth and seventh days, but showed a rise on the fifteenth day. At this point the second triple inoculation was given. The *B* titer had risen to a maximum when next examined on the seventh day. From the seventh to fortieth day the titer fell (87 per cent.)

30. That the maximum of the curve occurs on any given day, or that a negative phase is present or absent, can only be decisively stated when daily examinations of the blood are made, as in the case of the rabbit. In the case of the human subjects, conditions existed which rendered it impossible to take daily samples of blood. Accordingly, it is not possible in their case to determine with certainty the presence or absence of a negative phase on any particular day, or the exact position of the true maxima of their curves.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60
65

Curve 12

TABLE 15—DATA FROM WHICH CURVE 12 WAS PLOTTED

Day of Experiment	Standard Agglutinin Units		
	B Typhosus	B Paratyphosus A	B Paratyphosus B
1	0	0	0
6	Inoculation, 0 5 c c T A	B = 500 million T + 250 mi	llion A + 250 million B
10	0	0	0
13	3 22	57 0	0
21	32 25	622 0	53 3
21	Inoculation, 1 0 c c T A	B = 1,000 million T + 500	million A + 500 million B
28	541 0	1,010 0	950 0
35	432 0	539 0	622 0
38	192 0	442 0	304 0
61	64 8	103 0	120 0

The maxima of the *T*, *A*, and *B* curves appear to fall on the same day, instead of the more usual condition as seen in the other curves, namely, that the *B* curve commences its rise and attains its maximum later than the *T* and *A* curves This is perhaps apparent rather than real and may be due to the long intervals between examinations

R F D R—(Group 7, Curve 13) *The typhoid agglutinins* were not visibly affected by the *A B* inoculations On the second and fifth days after the first *T* inoculation there was still no rise of *T* agglutinins This is interesting in that both the *A* and *B* agglutinins showed rises of 68 and 65 per cent, respectively, on the second day after the first *T* inoculation On the tenth day the second *T* inoculation was given On the third day after this last *T* inoculation the *T* agglutinins showed a rise which reached its maximum on the twelfth day (after this last *T* inoculation) The *A* and *B* agglutinins also show rises of 2 and 75 per cent, respectively, on the twelfth day Whether the *A* and *B* curves would have shown a rise to a maximum before the *T* curves, if examinations had been made at shorter intervals, cannot be said with certainty, but judging from the other curves, it may be supposed that they would From the twelfth to the sixty-first day the *T* titer fell 94 per cent

The paratyphoid A agglutinins had not commenced to rise on the fifth day after the first *A B* inoculation but showed a marked rise on the seventh day, which was increased by the ninth day At this point the second *A B* inoculation was given The *A* titer continued to rise to a maximum four days later, that is, fourteenth day after the first inoculation A fall (7 per cent) occurs on the seventeenth day It may be assumed that the maximum of the *A* curves on the fourteenth day is that of the rise due to the first inoculation, even though it occurs four days after the second inoculation Whether the fall that is noted on the seventeenth day is the fall usually seen after the maximum of a single inoculation curve is attained, or whether it is the negative phase following the second inoculation, or whether again it is a combination of the two, cannot be decisively determined in this particular instance

The *A* titer has commenced its new rise due to the second inoculation and attained its maximum on the ninth day after the second inoculation (nineteenth day after the first inoculation) From this point until the twenty-first day the *A* titer falls 82 per cent where it is in equilibrium, for the titer shows no change on the twenty-third day At this point the first *T* inoculation is given This evidently stimulates the production of the *A* agglutinins for the

titer has risen (68 per cent) by the second day after this last inoculation A fall that is slightly greater than this rise is noted on the fifth day The second *T* inoculation is given on the ninth day Three days later no rise in *A* agglutinins is noted, in fact, they have decreased slightly since the last inoculation Whether this fall is a negative phase following the last *T* inoculation or whether it is the natural, gradual fall cannot be decisively stated Twelve days after this last *T* inoculation the titer has increased (2 per cent) From this point until the sixty-first day the *A* titer falls 60 per cent

TABLE 16—Data from which Curve 13 Was Plotted

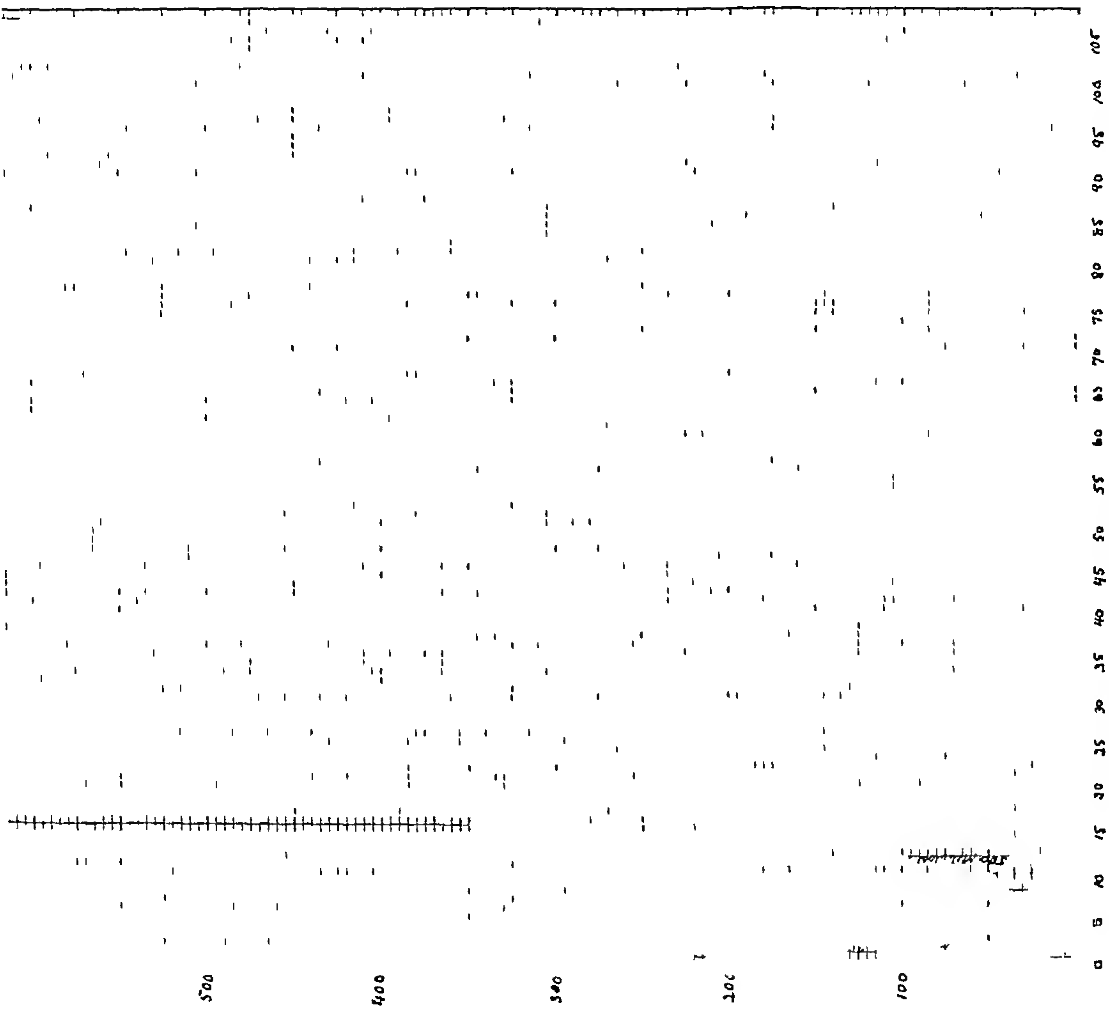
Day of Experiment	Standard Agglutinin Units		
	B Typhosus	B Paratyphosus A	B Paratyphosus B
1	0	0	0
3	Inoculated, 0 5 c c	A B = 250 million A + 250	million B
8	0	0	0
10	0	103 5	0
13	0	531 0 - 250 0	34 2
13	Inoculated, 1 0 c c	A B = 500 million A + 500	million B
17	0	1,035 0	56 0
20	0	950 0	71 5
22	0	1,428 0	71 5
27	0	1,100 0	285 0
29	0	1,032 0	357 0
31	0	590 0	264 0
34	0	250 0	132 2
36	0	250 0	142 3
36	Inocu	lated, 0 5 c c T = 500 milli	on T
38	0	421 0	235 0
41	0	235 0	107 2
45	Inocu	lated, 1 0 c c T = 1,000 mil	lion T
48	162 0	218 0	56 0
57	390 0	224 0	95 0
63	223 0	200 0	51 0
70	162 0	179 0	53 0
79	84 0	148 5	47 8
106	32 5	100 0	27 0

The paratyphoid B agglutinins had not commenced to rise on the fifth day after the first *A B* inoculation, but showed a very slight rise on the seventh day This was increased by the tenth day At this point the second *A B* inoculation was given The *B* titer continued to rise The plateau seen on the seventh to ninth day after the second inoculation may represent the maximum of the rise due to the first inoculation and the subsequent negative phase following the second inoculation The maximum of the rise due to the second inoculation was reached on the sixteenth day (after the second inoculation, the twenty-sixth day after the first inoculation) From this point

until the twenty-third day (after the second inoculation) the titer fell (45 per cent) On the twenty-third day the titer had risen slightly At this point the first *T* inoculation was given This evidently stimulated the *B* agglutinins, for by the second day after this inoculation the *B* titer had risen 55 per cent From this point until the fifth day after this last inoculation the

as that of the rise due to the second inoculation was attained on the sixteenth day By the twenty-fifth day after this last inoculation the *B* titer fell 53 per cent At this point the first *T* inoculation was given The *B* titer showed a slight fall by the third day after this first *T* inoculation, and a still greater drop by the fifth day On the tenth day the *B* titer showed a rise (150 per

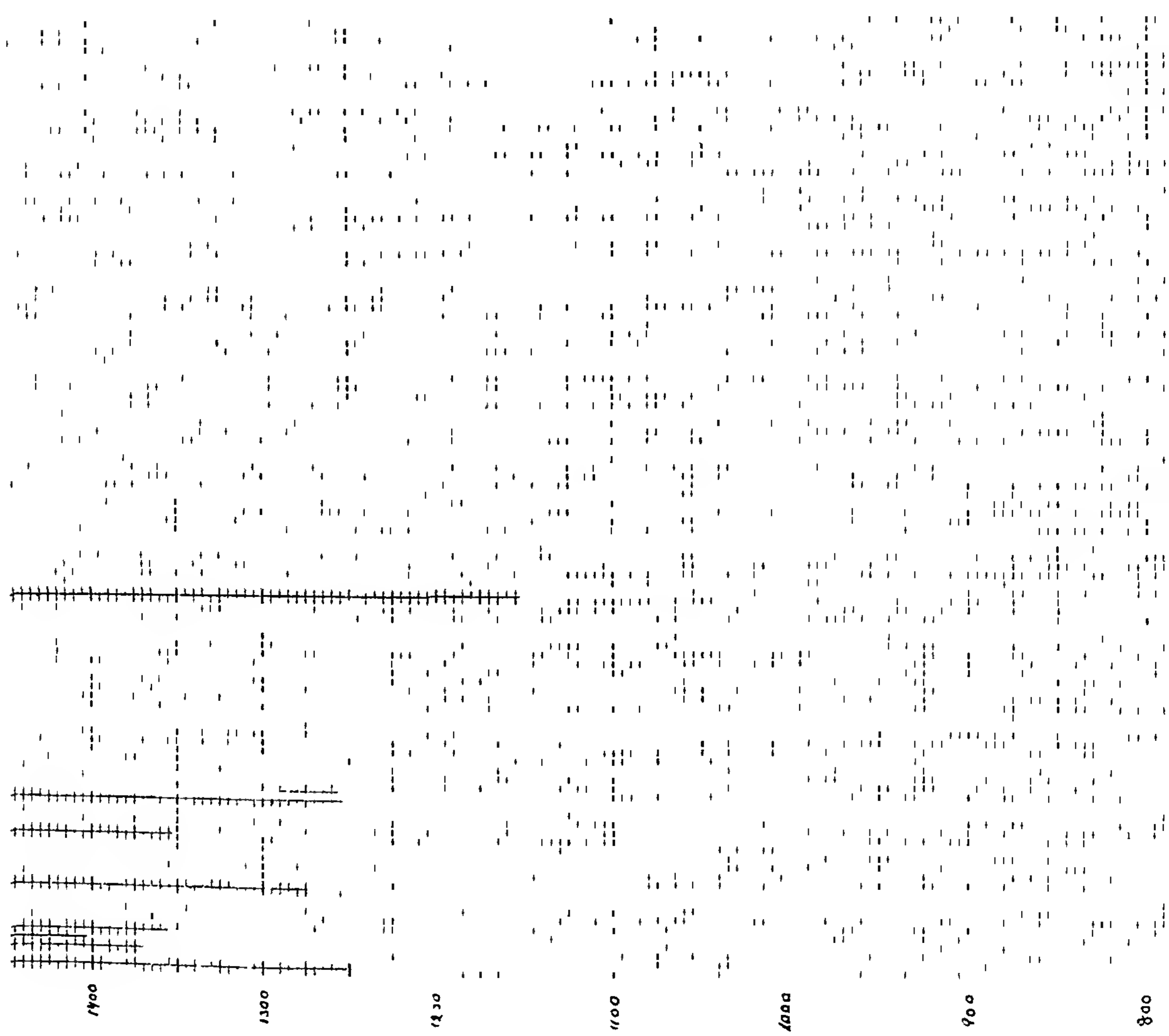
titer has risen (68 per cent) by the second day after this last inoculation A fall that is slightly greater than this rise is noted on the fifth da



Curve 13

had not commenced to rise on the fifth day after the first *A B* inoculation, but showed a very slight rise on the seventh day This was increased by the tenth day At this point the second *A B* inoculation was given The *B* titer continued to rise The plateau seen on the seventh to ninth day after the second inoculation may represent the maximum of the rise due to the first inoculation and the subsequent negative phase following the second inoculation The maximum of the rise due to the second inoculation was reached on the sixteenth day (after the second inoculation, the twenty-sixth day after the first inoculation) From this point

until the twenty-third day (after the second inoculation) the titer fell (45 per cent) On the twenty-third day the titer had risen slightly At this point the first *T* inoculation was given This evidently stimulated the *B* agglutinins, for by the second day after this inoculation the *B* titer had risen 55 per cent From this point until the fifth day after this last inoculation the



as that of the rise due to the second inoculation was attained on the sixteenth day By the twenty-fifth day after this last inoculation the *B* titer fell 53 per cent At this point the first *T* inoculation was given The *B* titer showed a slight fall by the third day after this first *T* inoculation, and a still greater drop by the fifth day On the tenth day the *B* titer showed a rise (150 per

titer has risen (68 per cent) by the second day after this last inoculation A fall that is slightly greater than this rise is noted on the ... second *T* inoculation is ...

[illegible]

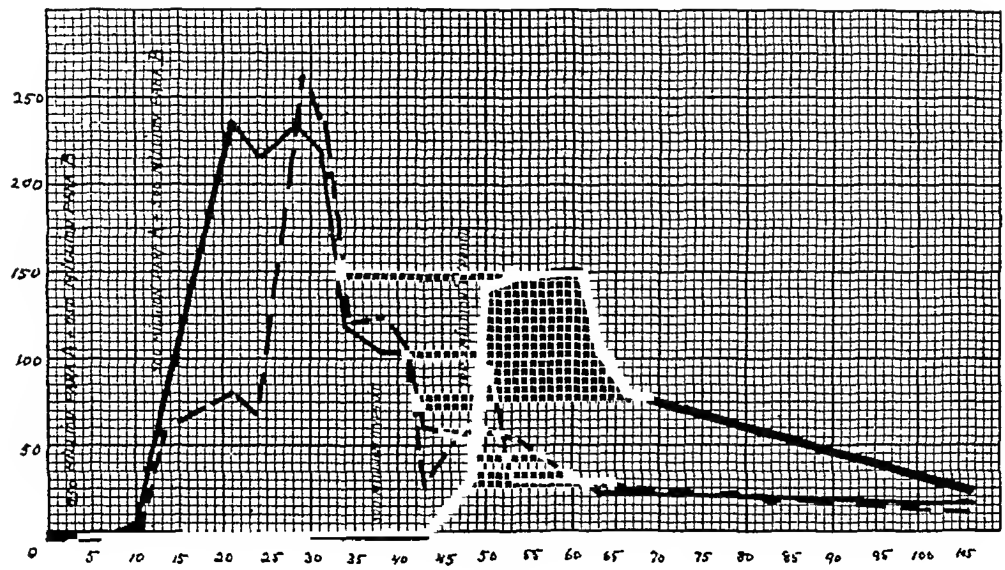
inoculation was given The *B* titer continued to rise The plateau seen on the seventh to ninth day after the second inoculation may represent the maximum of the rise due to the first inoculation and the subsequent negative phase following the second inoculation The maximum of the rise due to the second inoculation was reached on the sixteenth day (after the second inoculation, the twenty-sixth day after the first inoculation) From this point

until the twenty-third day (after the second inoculation) the titer fell (45 per cent) On the twenty-third day the titer had risen slightly At this point the first *T* inoculation was given This evidently stimulated the *B* agglutinins, for by the second day after this inoculation the *B* titer had risen 55 per cent From this point until the fifth day after this last inoculation the *B* titer fell 64 per cent The second *T* inoculation was given on the tenth day On the third day after this second inoculation the *B* titer showed a distinct drop (20 per cent), but no examination was possible on the tenth when the second *T* inoculation was given, owing to the loss of the blood specimen by the breaking of a faulty centrifuge tube It is therefore impossible to decide in this instance whether this further fall in titer just mentioned was a true negative phase or whether it represented the normal fall in titer On the twelfth day after this second *T* inoculation, the *B* titer showed a rise of 75 per cent, evidently in response to the stimulation of the last *T* inoculation By the eighteenth day after this second *T* inoculation the *B* titer fell 46 per cent As the subsequent fall in titer was but gradual from this point until the sixty-first day (after the second *T* inoculation) it may be assumed that the curve had reached its point of equilibrium

H W T—(Group 7, Curve 14) *The typhoid agglutinins* were not apparently affected by either of the *A B* inoculations and did not show a rise until the tenth day after the first *T* inoculation At this point the second *T* inoculation was given The *T* titer shows a marked rise on the second day after this last inoculation, reaching a maximum on the thirteenth day From this point until the eighteenth day the curve shows a fall of 43 per cent When next examined on the fifty-eighth day the *T* titer had fallen an additional 40 per cent

The paratyphoid A agglutinins had not commenced to rise on the fifth day after the first *A B* inoculation but showed a rise on the seventh day which had greatly increased by the tenth day At this point the second *A B* inoculation was given When next examined on the eighth day after this last inoculation the *A* titer had risen 300 per cent, which may possibly be the maximum of the rise due to the first inoculation On the eleventh day the *A* titer had fallen slightly (possibly a negative phase following the second inoculation) but regained its former height on the sixteenth day (possibly the maximum of the rise due to the second *A B* inoculation) From this point until the twenty-fifth day the *A* titer fell 57 per cent At this point the first *T* inoculation was given By the third day the *A* titer had risen slightly, evidently stimulated by the *T* inoculation From this point until the tenth day the *A* titer fell 48 per cent At this point the second *T* inoculation was given The *A* titer showed a rise of 75 per cent on the second day after this inoculation From this point until the fifth day the *A* titer fell 85 per cent The curve then shows but a small decrease until the eighteenth day, indicating that the titer had reached its point of equilibrium When next examined on the fifty-eighth day the *A* titer showed an additional fall of 11 per cent

The paratyphoid B agglutinins had not commenced to rise on the fifth and seventh days after the first *A B* inoculations, but showed a rise on the tenth day At this point the second *A B* inoculation was given By the eighth day after this last inoculation, that is, the eighteenth day after the first inoculation, the *B* titer had risen 117 per cent, which may be considered as the maximum of the rise due to the first inoculation On the eleventh day after the second inoculation a fall was noted which may represent the negative phase following the second inoculation A rise to a maximum which may be considered as that of the rise due to the second inoculation was attained on the sixteenth day By the twenty-fifth day after this last inoculation the *B* titer fell 53 per cent At this point the first *T* inoculation was given The *B* titer showed a slight fall by the third day after this first *T* inoculation, and a still greater drop by the fifth day On the tenth day the *B* titer showed a rise (150 per



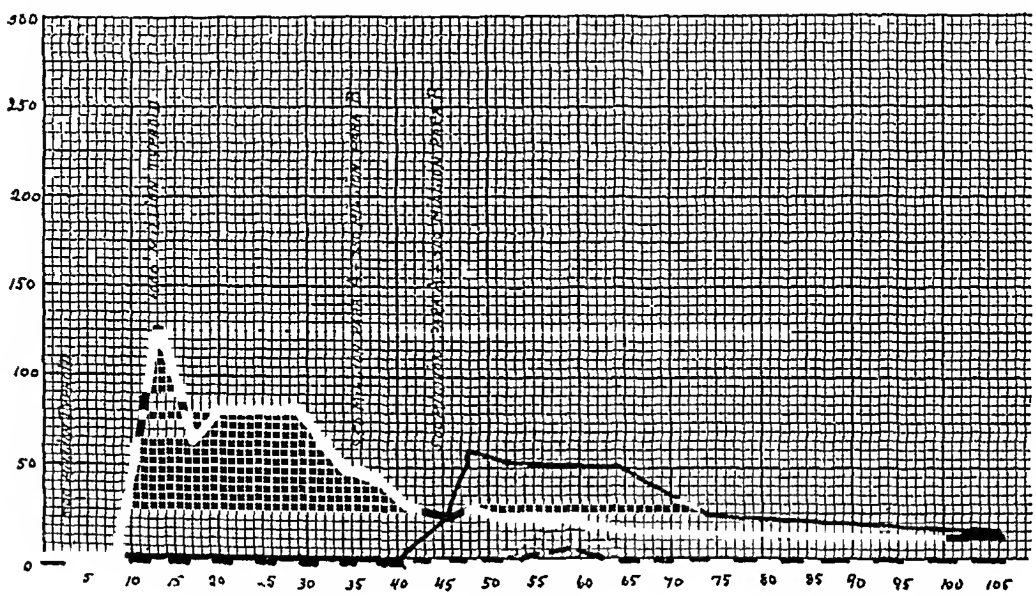
Curve 14

TABLE 17—Data from which Curve 14 Was Plotted

Day of Experiment	Standard Agglutinin Units		
	B Typhosus	B Paratyphosus A	B Paratyphosus B
1	0	0	0
3	Inoculated, 0 5 c c A B = 250 million A + 250 million B		
8	0	0	0
10	0	2 85	0
13	Inoculated, 1 0 c c A B = 500 million A + 500 million B		
21	0	235 0	128 0
24	0	215 0	118 7
29	0	235 0	265 0
31	0	218 0	237 0
34	0	118 0	122 0
38	0	102 7	125 0
38	Inoculated, 0 5 c c T = 500 million T		
41	0	103 0	107 0
43	0	59 0	25 0
48	27 7	53 0	64 0
48	Inoculated, 1 0 c c T = 1,000 million T		
50	139 0	98 5	59 0
53	144 0	29 5	53 2
61	149 0	28 5	25 5
63	104 0	24 2	27 0
66	84 0	24 2	25 0
106	24 2	18 3	10 85

cent) Whether or not this rise would have been found to occur earlier if the intervals between examinations had been shorter cannot be decisively stated At this point the second T inoculation was given The B titer shows no further rise Whether or not a rise may have occurred during one of the intervals when the blood was not examined, cannot be decisively stated By the thirteenth day after this last T inoculation the B titer had fallen 66 per cent and as it showed no change from this point until the eighteenth day it may be assumed that this curve had reached its point of equilibrium When next examined on the fifty-eighth day the B titer had fallen an additional 14 per cent

T P—(Group 8, Curve 15) *The typhoid agglutinins* had not commenced to rise on the fifth day after the first T inoculation, but showed a rise on the seventh day which was greatly increased by the tenth day, which appears to have been the maximum At this point the second T inoculation was given On the fourth day after this last inoculation the T titer fell (50 per cent , that is, a negative phase) On the seventh day the titer showed a rise of 27 per cent The curve shows no change when examined on the eleventh and sixteenth days From the sixteenth to twenty-third day the T titer fell 41



Curve 15

per cent At this point the first A B inoculation was given The T titer showed only a small drop (6 per cent) By the fifth day a further drop of 36 per cent had occurred By the tenth day the titer had fallen still farther At this point the second inoculation is given On the third day after this last inoculation the T titer evidently stimulated by the A B inoculation shows a rise of 19 per cent From this point until the nineteenth day the T titer fell 37 per cent As the titer showed but a very gradual fall from this point until the sixty-first day after the last inoculation, it may be assumed that it had reached its point of equilibrium

The paratyphoid A agglutinins did not show a rise until the fifth day after the first A B inoculation, which was greatly increased by the tenth day At this point the second A B inoculation was given The titer showed a rise of 150 per cent by the third day after this last inoculation, which appears to be the maximum By the seventh day a fall of 14 per cent had occurred From this point until the nineteenth day the curve showed little change From the nineteenth to twenty-ninth day a fall of 52 per cent had occurred When next examined on the sixty-first day after the last inoculation an additional fall of 28 per cent had occurred

TABLE 18—Data from which Curve 15 Was Plotted

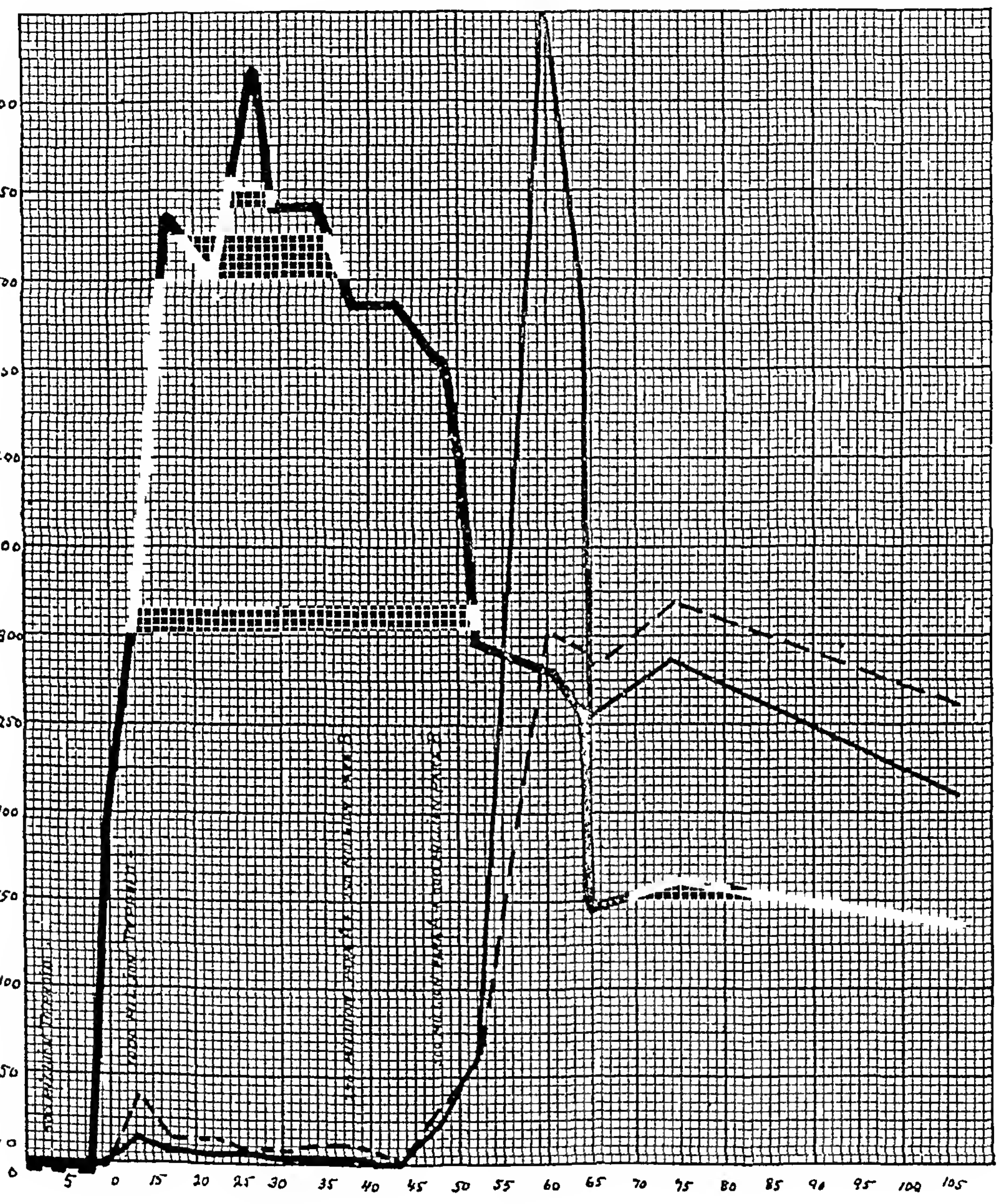
Day of Experiment	Standard Agglutinin Units		
	B Typhosus	B Paratyphosus A	B Paratyphosus B
1	0	0	0
3	Inoculated, 0 5 c c T = 500 million T		
8	0	0	0
10	40 3	0	0
13	126 0	0	0
13		Inoculated, 1,000 million T	
17	63 0	0	0
20	80 1	0	0
24	80 1	0	0
29	32 5 - 80 1	0	0
31	64 9	0	0
34	48 6	0	0
36	46 5	0	0
36	Inoculated, 0 5 c c A B = 250 million A + 250 million B		
38	43 0	0	0
41	29 1	2 06	0
45	22 6	23 6	0
45	Inoculated 1 0 c c A B = 500 million para A + 500 million para B		
52	27 0	59 0	0
52	22 0 - 128 0	51 5	0
59	23 7 20 2	51 5	5 31
64	14 15	50 0	0
74	13 8	24 0	0
106	11 9	24 0	0

The paratyphoid B agglutinins did not show a rise until the fourteenth day after the second *A B* inoculation, which appears to be the maximum By the nineteenth day the *B* titer had fallen to the base line of normal agglutination where it remained for all subsequent examinations The only rise of the agglutinins of the first organism (that is, *T*) which can be attributed to the *A B* inoculations was one that occurred on the same day as the maximum of the *A* curve (one of the organisms inoculated later) The very late and slight rise of the *B* curve is anomalous and is somewhat difficult of explanation

E A W—(Group 8, Curve 16) In Curve 16, E A W gave no history of a previous infection or inoculation with *B typhosus, B paratyphosus A* or *B paratyphosus B,* although from the readiness with which the *A* and *B* agglutinins respond to the *T* inoculation, it might appear there had been some previous undiagnosed infection by these two organisms, unless we have here an instance of abnormal sensitiveness of the mechanism for the formation of antibodies

The typhoid agglutinins had not commenced to rise on the fifth day after the first *T* inoculation, but showed a marked rise by the seventh day This

was further increased by the tenth day At this point the second T inoculation was given By the fourth day after this last T inoculation the T titer had risen 77 per cent By the ninth day the T titer showed a fall of 6 per cent The curve up to this point may be interpreted variously As has been noted above, the maximum of the rise due to the first inoculation may occur in one of three places (1) before the second inoculation, (2) after the second



Curve 16

inoculation, or (3) may be fused, as it were, with the rise due of the second inoculation, depending on the length of the interval between the two inoculations In this case, it appears that the second of these possibilities has occurred and that the T apex on the fourth day after the second T inoculation is the maximum of the rise due to the first inoculation and that the fall noted on the ninth day after the second inoculation is the negative phase following the second inoculation By the fourteenth day after the second inoculation the new rise had commenced and had attained its maximum By the sixteenth day the T titer had fallen (12 per cent) The curve shows no

TABLE 19—DATA FROM WHICH CURVE 16 WAS PLOTTED

Day of Experiment	Standard Agglutinin Units		
	B Typhosus	B Paratyphosus A	B Paratyphosus B
1	0	0	0
3	Inoculation, 0 5 c c T = 500 million B typhosus		
8	0	0	0
10	200	2 85	1 43
13	298	15 0	37 5
13	Inoculation, 0 5 c c T = 1,000 million B typhosus		
17	535	7 15	12 8
22	500	5 7	14 15
27	620	5 0	5 7
29	540	3 78	5 7
31	540	3 78	6 4
34	540	3 55	9 5
38	486	3 55	11 9
38	Inoculation, 0 5 c c A B = 250 million para A + 250 million para B		
41	486	2 29	5 7
43	486	1 19	2 86
48	454	0 25	27 4
48	Inoculation, 1 0 c c A B = 500 million para A + 500 million para B		
50	405	44 1	43 0
52	296	59 0	62 1
60	278	648 0 768 0	302 0
64	255	476 0	292 0
65	148	252 0	284 0
74	162	286 0	319 0
106	138	210 0	263 0

change on the eighteenth and twenty-first days By the twenty-fifth day the *T* titer had fallen another 8 per cent At this point the first *A B* inoculation was given

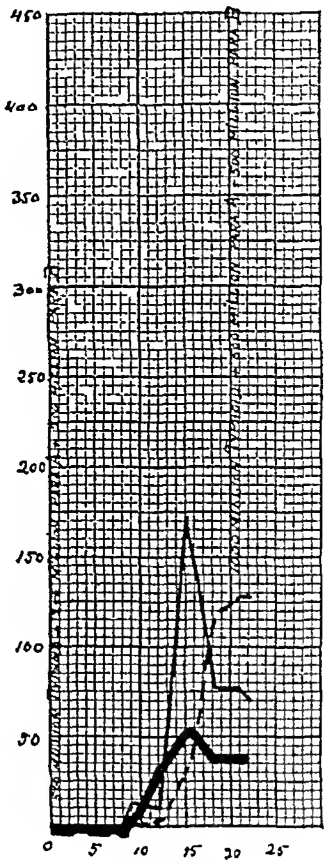
The *T* agglutinins were possibly affected by this first *A B* inoculation for they showed no change (that is, did not continue their natural fall) when examined on the third and fifth days (after this first *A B* inoculation) On the tenth day the *T* titer had fallen 6 per cent At this point the second *A B* inoculation was given but no effect was seen in the *T* titer From this point until the seventeenth day (after this last inoculation) the *T* titer fell (65 per cent) The fall in titer from the seventeenth to fifty-eighth day was very gradual, indicating that it had reached its point of equilibrium

The paratyphoid A agglutinins did not commence to rise until the seventh day after the first *T* inoculation and reached a maximum on the tenth day At this point the second *T* inoculation was given The *A* titer had fallen 50 per cent by the fourth day after this last inoculation From this point until the twenty-fifth day after this last *T* inoculation the *A* titer showed little

change At this point the first *A B* inoculation was given On the third and fifth days after this a drop was seen (that is, negative phase) On the tenth day a marked rise had occurred At this point the second *A B* inoculation was given The curve continued its rise reaching its maximum on the twelfth day From the twelfth to seventeenth day a rapid fall (65 per cent) occurred The fall in titer from the seventeenth to twenty-sixth day was very gradual, indicating that it had reached its point of equilibrium

The paratyphoid B agglutinins behaved in exactly the same way as the *T* and *A* agglutinins, their maxima and negative phases occurring on the same days

W C C—(Group 9, Curve 17) *The typhoid agglutinins* first show a slight rise on the eighth day after the first triple inoculation and reach their maximum on the fourteenth day On the seventeenth day a fall (25 per cent) is recorded On the twentieth day no change in the typhoid titer is noted The



Curve 17

second inoculation is given at this point On the following day no change is noted (that is, no negative phase) It was impossible to examine the blood for an interval of thirty-eight days By this time the *T* titer had fallen and any rise due to the second triple inoculation was missed

The paratyphoid A agglutinin, like the T agglutinin, show a rise on the eighth day after the first inoculation, which reaches its maximum also on the fourteenth day By the seventeenth day the titer has fallen (56 per cent) and shows no change on the twentieth day At this point the second inoculation is given On the following day a slight fall in titer (that is, a negative phase) is noted It was impossible to examine the blood for an interval of thirty-eight days By this time the *A* titer had fallen and any rise due to the second inoculation was missed

TABLE 20—DATA FROM WHICH CURVE 17 WAS PLOTTED

Day of Experiment	Standard Agglutinin Units		
	B Typhosus	B Paratyphosus A	B Paratyphosus B
1	0	0	0
1	Inoculated, 0 5 c c T A B = 500 million T + 250 million A + 250 million B		
3	0	0	0
9	1 3	11 8	1 43
12	32 4	9 8	2 85
15	53 0	172 0	31 9
18	38 9	76 1	53 0 96 0 119 0
21	37 1	76 1	127 8
21	Inoculated, 1 0 c c T A B = 1,000 million T + 500 million A + 500 million B		
22	37 1	71 5	127 8
60	28 0	53 0	600 0

The paratyphoid B agglutinins showed a very slight rise on the eighth day after the first inoculation, which reached its maximum on the twentieth day, when the second inoculation was given The titer shows no change the next day It was impossible to examine the blood for an interval of thirty-eight days The *B* titer then showed a marked rise It will be noted that in common with most of the other experiments the *B* curve attained its maximum later than the *T* and *A* curves

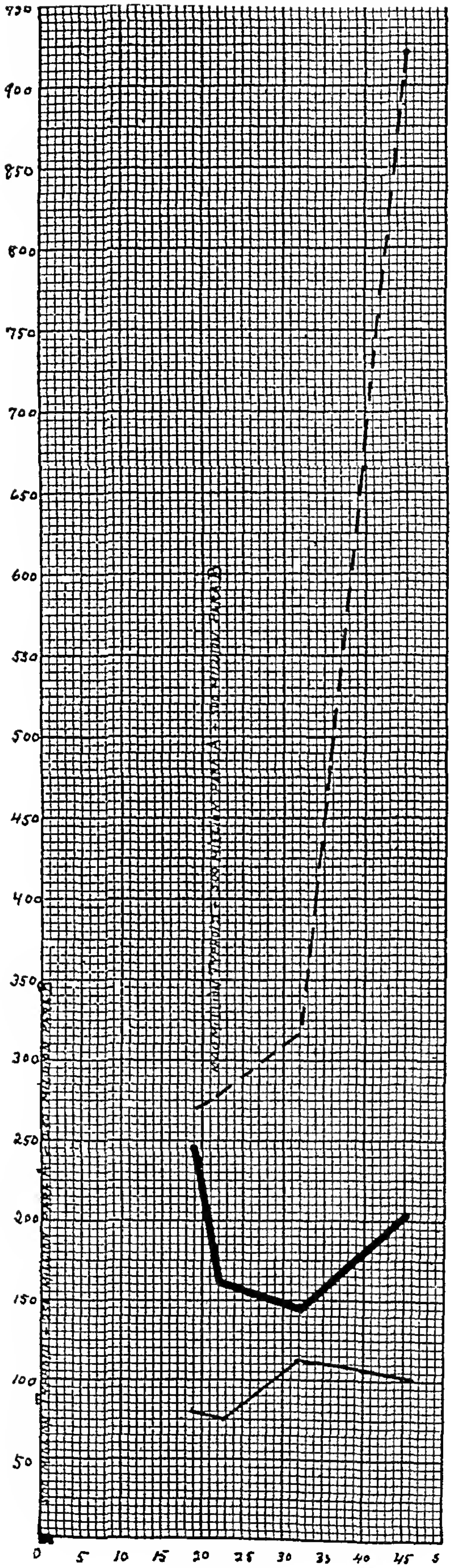
F H M—(Group 9, Curve 18) When first examined on the nineteenth day after the first triple inoculation the *typhoid agglutinins* had evidently attained their maximum, for on the twenty-first day the titer had fallen (33 per cent) At this point the second inoculation was given

The *T* titer showed a fall (8 per cent, possibly a negative phase) when examined on the tenth day (after the second inoculation) On the twenty-third day a rise in the *T* titer (36 per cent) was noted

The paratyphoid A agglutinins, like the *T* agglutinins, have reached their maximum on the nineteenth day and show a fall (5 per cent) on the twenty-first day At this point the second inoculation was given By the tenth

TABLE 21—DATA FROM WHICH CURVE 18 WAS PLOTTED

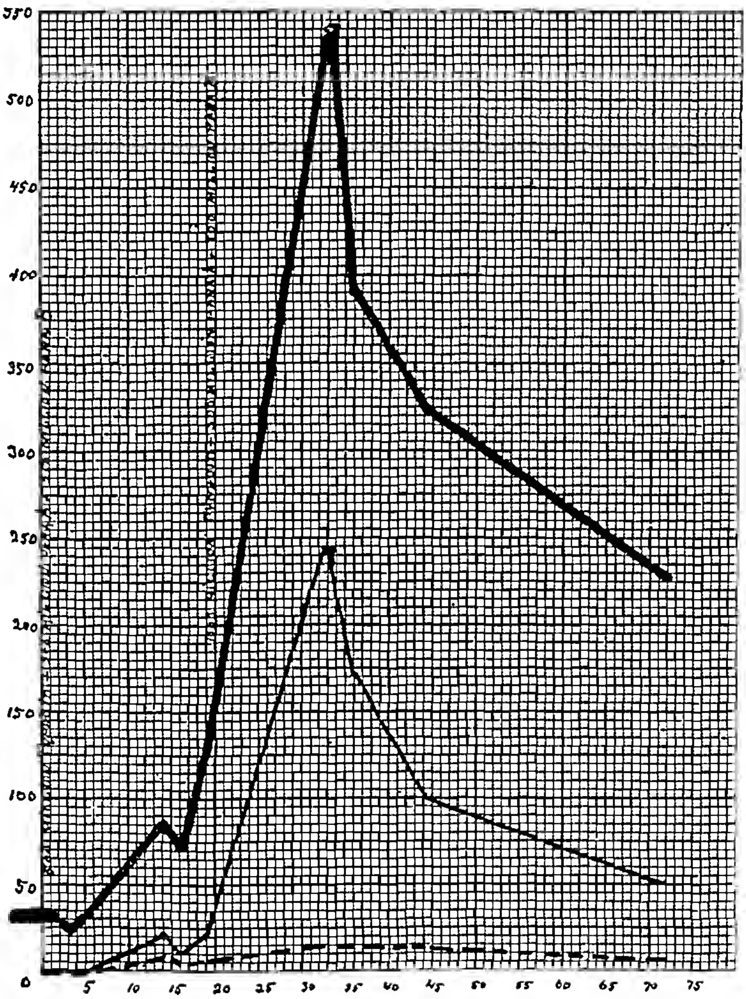
Day of Experiment	Standard Agglutinin Units		
	B Typhosus	B Paratyphosus A	B Paratyphosus B
1	0	0	0
1	Inoculated 0 5 c c T A B = 500 million T + 250 million A + 250 million B		
19	244 0	80 0	271 5
22	162 1	75 6	281 0
22	Inoculated, 1 0 c c T A B = 1 000 million T + 500 million A + 500 million B		
32	148 0	114 0	320 0
45	202 0	100 0	920 0



Curve 18

day after the second inoculation the *A* titer had risen (40 per cent) By the twenty-third day a fall of 10 per cent had occurred

The paratyphoid B agglutinins showed a marked rise on the nineteenth day, which is further increased on the twenty-first The *B* titer showed a marked rise on the tenth day after the second inoculation, which was greatly increased by the twenty-third day It will also be noted here that the *B* curve attains its maximum last



Curve 19

J W—(Group 10, Curve 19) *The typhoid agglutinins* when examined four months after the last inoculation had fallen to 39 standard agglutinin units, this was the point of equilibrium, for examinations made one month and six months later showed only a small decrease After this last examination, that is, ten months after the last inoculation, the first triple inoculation was given Two days later a negative phase was seen *On the fifth day* the typhoid titer had commenced to rise, continuing until the fourteenth day On the sixteenth day a fall is seen similar to that seen in the *A* and *B* curves at this point, but on the nineteenth day the curve continues its rise At this point the second triple inoculation was given The typhoid titer had reached its maximum by the fourteenth day after this last inoculation From the fourteenth to fifty-first day the titer fell (60 per cent), the fall at first being rapid but later becoming more gradual

The paratyphoid A agglutinins did not show a rise until the fourteenth day after the first triple inoculation. After a fall on the sixteenth day similar to that seen in the *T* and *B* curves at this point, the titer showed a further rise on the nineteenth day. At this point the second triple inoculation was given. The titer had reached its maximum by the fourteenth day after this last inoculation. From the fourteenth to fifty-first day there is a fall of 80 per cent.

The paratyphoid B agglutinins do not show a rise until the fourteenth day after the first triple inoculation. On the sixteenth day a fall is seen similar to that seen in the *T* and *A* curves at this point. On the nineteenth day the curve has recommenced its rise. At this point the second triple inoculation

TABLE 22.—Data from which Curve 19 Was Plotted

Day of Experiment	Standard Agglutinin Units		
	B Typhosus	B Paratyphosus A	B Paratyphosus B
1	30 0*	0	0
1	Inoculation, 0 5 c c T A	B = 500 million T + 250 m	illion A + 250 million B
3	24 20	0	0
6	32 4	0	0
15	84 2	20 7	31 25
17	65 0	10 82	21 0
20	130 0	22 6	30 0
20	Inoculation, 1 0 c c T A	B = 1,000 million T + 500	million A + 500 million B
24	54 1	244 0	12 78
27	390 0	171 5	9 58 - 12 78
45	325 0	100 0	11 18
71	227 0	50 0	5 58

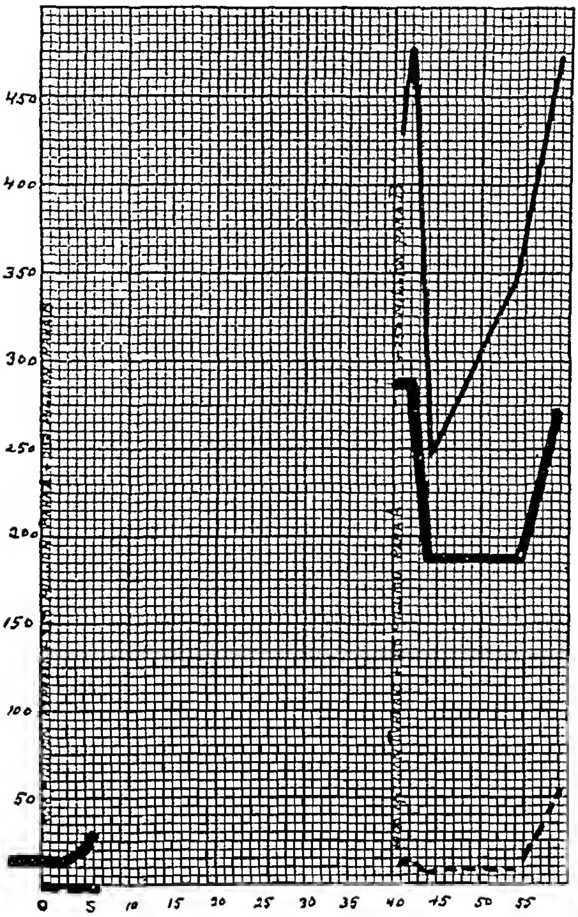
* Immunized with two doses of B typhosus vaccine (first, 500 million, second, 1,000 million) ten months previous to present experiment.

is given. The titer has reached its maximum by the fourteenth day after this last inoculation. From the fourteenth to twenty-fifth day there is little change showing that the curve has reached its point of equilibrium. From the twenty-fifth to fifty-first day the *B* titer shows a fall of 45 per cent.

This curve is of interest for it plainly shows a negative phase in the persistent typhoid agglutinins resulting from the first triple inoculation. It cannot be contended here, as might be done in the case of falling curves, that this fall was the normal fall in titer, for the typhoid titer had been practically stationary for over six months, three examinations at intervals of two months having shown only a very slight gradual fall.

E. H. N.—(Group 10, Curve 20.) Thirty-two months after the last *T* inoculation, the *typhoid agglutinins* had fallen to 13.8 standard agglutinin units. At this point the first triple inoculation was given. The typhoid titer had risen 17 per cent the third day (no negative being seen), and by the fifth day the typhoid agglutinins were double the amount recorded at the time of the first triple inoculation. I shall discuss later the significance of this quick response to reinoculation by the typhoid agglutinins in previously inoculated men.

The next examination made on the fortieth day showed that the typhoid titer had risen 960 per cent. At this point the second triple inoculation was



Curve 20

TABLE 23—DATA FROM WHICH CURVE 20 WAS PLOTTED

Day of Experiment	Standard Agglutinin Units		
	B Typhosus	B Paratyphosus A	B Paratyphosus B
1	13 8*	0	0
1	Inoculated, 0 5 c c T A	B = 500 million T + 250 m	illion A + 250 million B
4	16 25	0	0
6	27 0	0	0
41	260 0	427 0	10 2
41	Inoculated, 1 0 c c T A	B = 1,000 million T + 500	million A + 500 million B
42	260 0	475 0	12 8
44	162 1	244 0	5 1
54	162 1	344 0	6 4
59	242 0	475 0	55 5

* Immunized with three doses of B typhosus vaccine (first, 500 million, second, 1 000 million, third, 1,000 million) at weekly intervals, thirty two months previous to present experiment

given The next day revealed no change in typhoid titer, but on the third day after the last inoculation the typhoid titer had fallen (62 per cent, that is, a negative phase) On the thirteenth day the titer showed no change, but on the eighteenth day it had risen 30 per cent

The paratyphoid A agglutinins showed no rise for the first five days, but when examined on the fortieth day a large rise was noted At this point the second triple inoculation was given The titer showed a slight rise on the following day A fall of 48 per cent was noted on the second day (negative phase) On the thirteenth day the *A* titer showed a rise of 26 per cent, which was increased to 47 per cent by the eighteenth day

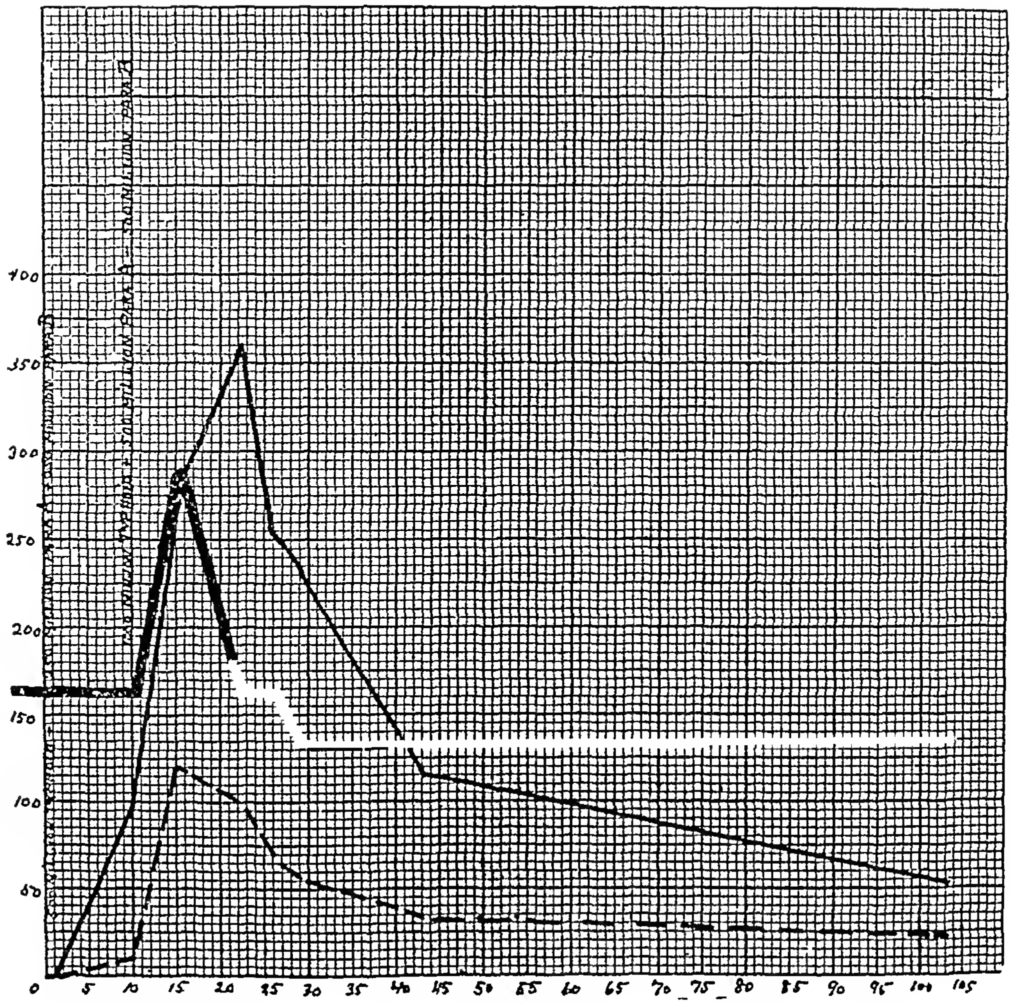
The paratyphoid B agglutinins like the *A* agglutinins had not commenced to rise during the first five days When examined on the fortieth day the titer showed a marked rise The second triple inoculation was given at this point No change in titer was noted on the next day On the second day a fall of 52 per cent is shown (negative phase) On the thirteenth day the *B* titer shows a rise which is much increased by the eighteenth day

E F H—(Group 10, Curve 21) When examined twenty-two months after the last *T* inoculation the *T* agglutinin titer had fallen to 161 standard agglutinin units The first triple inoculation was then given The blood was next examined after an interval of nine days and no change in titer was found Whether or not the curve had remained stationary during this interval or whether a negative phase had occurred, or whether a quick rise followed by a fall had taken place, cannot be determined from these observations As it stands this curve would appear to form an exception to the general conclusion arrived at below, that the agglutinins in a previously inoculated individual react more quickly to reinoculation than do the agglutinins of an individual not previously inoculated Another explanation is, however, more probable as will be seen later At this point, that is, the ninth day after the first triple inoculation, the second inoculation was given On the fifth day thereafter, the typhoid titer showed a rise of 82 per cent A fall of equal amount followed by the twelfth day Now if the blood had not been examined for an interval of twelve days after the second triple inoculation, the curve would then have appeared to have remained stationary, though, as a matter of fact, it had undergone a marked rise and fall, for the rise would have been missed in the interval Hence it is possible to suppose that a similar condition following the first triple inoculation was missed in the interval between the examinations, and that instead of a stationary curve as we appear to have, the rise and subsequent fall were completed between the two successive observations *T* titer then gradually falls until the nineteenth day From this point the curve appears to be in equilibrium, for little change is noted

The paratyphoid A agglutinins show a rise on the ninth day (after the first triple inoculation) At this point the second triple inoculation was given The paratyphoid *A* curve continues to rise unbroken (no negative phase being seen, although an examination was made two days after the second inoculation) The maximum was attained on the twelfth day The curve is one of the few cases in which it appears that the paratyphoid *A* curve has reached its maximum later than the *T* or *B* curves This appearance, however, may be artificial and due to the fact that the three actual maxima may all have occurred during the interval from the fifth to fourteenth day from the second triple inoculation, so that all are already falling at the next observation

In the twelfth to ninety-third day, the *A* titer fell 85 per cent, the fall at first being rapid and later becoming more gradual

The paratyphoid B agglutinins show a slight rise on the ninth day after the first triple inoculation At this point the second triple inoculation is given The *B* titer reaches its maximum on the fifth day after the second triple inoculation From this point to the ninety-third day the curve falls (75 per cent), the drop at first being rapid and later being more gradual



Curve 21

TABLE 24—Data from which Curve 21 Was Plotted

Day of Experiment	Standard Agglutinin Units		
	B Typhosus	B Paratyphosus A	B Paratyphosus B
1	161 1*	0	0
1	Inoculation, 0 5 c c T A B = 500 million T + 250 million A + 250 million B		
10	161 1	94 1	10 7
10	Inoculation, 1 0 c c T A B = 1,000 million A + 500 million A + 500 million B		
15	286 0	285 0	119 0
22	161 1	357 5	100 0
26	162 1	251 0	71 5
29	130 0	232 0	57 0
43	130 0	118 0	32 5
103	138 0	50 0	23 6

* Immunized with three doses of B typhosus vaccine (first, 500 million, second, 1,000 million, third, 1,000 million) twenty two months previous to present experiment

The fact that the *B* agglutinins attain their maximum on the same day as the *T* agglutinins is worthy of note, although it must not be forgotten that this as well as the fact that the respective maxima have occurred between the ninth and the fourteenth day (from the second triple inoculation) and so have been missed

A D G—(Group 11, Curve 22) *The typhoid agglutinins* eight months after the first inoculation (that is, the *T* inoculation) had fallen to 10 standard agglutinin units When next examined, six months later, the *T* titer had not appreciably changed At this point the first triple inoculation was given Six days after this the *T* titer had risen 2,000 per cent This quick rise of the *T* agglutinins is of interest, for in men not previously inoculated with *T*, the *T* titer does not begin to rise until the seventh to eighth day, and the maximum is not attained until about the fourteenth to twenty-first day The significance of this will be discussed later

TABLE 25—Data from which Curve 22 Was Plotted

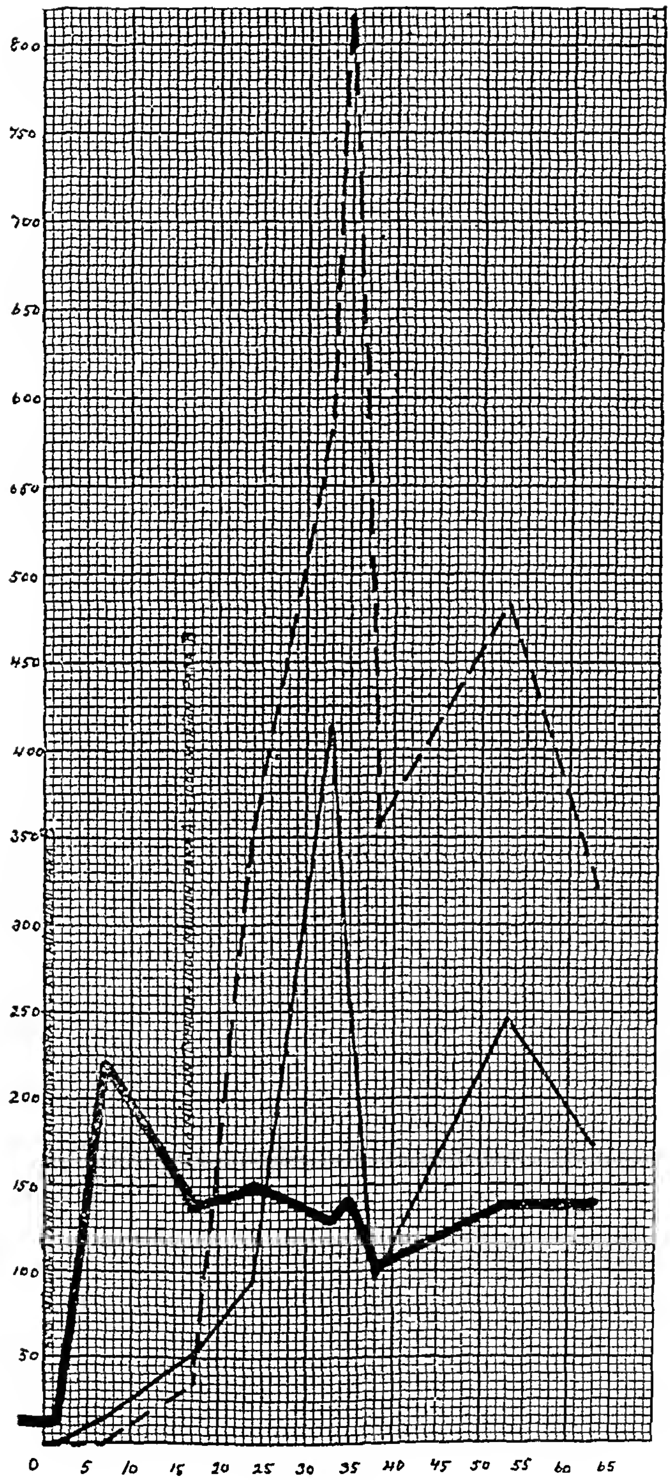
Day of Experiment	Standard Agglutinin Units		
	B Typhosus	B Paratyphosus A	B Paratyphosus B
1	10 22*	0	0
1	Inoculation, 0 5 c c T A	B = 500 million T + 500 m	illion A + 500 million B
7	219 0	13 2	0
17	138 0	51 6	35 6
17	Inoculation, 1 0 c c T A B	= 1,000 million T + 1,000	million A + 1,000 million B
24	148 0	94 5	356 0
33	130 0	412 0	592 0
35	142 1	252 0	817 0
38	104 0	98 0	356 0
53	138 0	245 0	476 0
63	138 0	172 0	320 0

* Immunized with one dose of B typhosus vaccine (1,000 million) fourteen months previous to present experiment

On the sixteenth day (after the first triple inoculation) the *T* titer had fallen (33 per cent) At this point the second triple inoculation was given The titer had risen 7 per cent when examined seven days later On the sixteenth day after the second triple inoculation the titer had fallen (13 per cent) On the eighteenth day after the second triple inoculation the titer shows a new rise (9 per cent) On the twenty-first day the titer has again fallen (26 per cent) From this point the curve is irregular and difficult of explanation, but judging from the fact that the *A* and *B* curves show the same phenomena, they must be significant On the eighteenth day (after the second triple inoculation) the *T* curves show a new rise, to be followed on the thirty-sixth day by a decided rise The titer shows no change on the forty-sixth day The decided rise from the twenty-first to the thirty-sixth day (after the second triple inoculation) is somewhat difficult to explain, but since the same phenomenon is recorded in both the *A* and *B* curves, it must be significant

The paratyphoid A agglutinins show a slight rise on the sixth day which reaches its maximum on the sixteenth day

At this point the second inoculation is given The titer shows an increase on the seventh day which reaches its maximum on the sixteenth day after the


800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
5
10
15
20
25
30
35
40
45
50
55
60
65

Curve 22

second inoculation From the sixteenth to eighteenth day (after the second triple inoculation, thirty-second to thirty-fourth day after the last triple inoculation), the *A* titer falls 39 per cent

A further fall (36 per cent) recorded during the next three days (thirty-seventh day after the first triple inoculation and twenty-first day after the second triple inoculation) On the thirty-sixth day after the second triple inoculation a rise (140 per cent) is noted, the same phenomenon as has been recorded in this curve for the *T* agglutinins On the forty-sixth day from the second triple inoculation the *A* titer has fallen 30 per cent

A rise in the *paratyphoid B titer* was not recorded until the sixteenth day after the first triple inoculation At this point the second triple inoculation was given The curve continues its rise, showing no break in continuity (this may be an artefact due to the fact that no examination was made for seven days after the second triple inoculation) and reaches its maximum on the eighteenth day after the second triple inoculation In common with the majority of the other curves, the *B* is the last to attain its maximum A fall in titer (56 per cent) is recorded on the thirty-seventh day after the first triple inoculation (twentieth day after the second triple inoculation) On the thirty-sixth day after the second triple inoculation a rise in titer (30 per cent) similar to that seen in the *T* and *A* curves on the same days, is noted A fall (33 per cent) then takes place (forty-sixth day after the second inoculation) similar to that noted for the *A* titer for the same days

W C D—(Group 11, Curve 23) Twenty months after the last *T* inoculation the *number of typhoid standard agglutinin* units had fallen to 7 The *T* titer had fallen to 4 standard agglutinin units when examined five months later At this point (that is, twenty-fifth month after the last *T* inoculation) the first triple inoculation was given The same quick rise as has been described above (Curves 19, 20 and 22) in men previously inoculated with *T* is again well brought out in this curve, for on the sixth day after the first triple inoculation there is a rise of over 180 per cent The *T* titer reaches its maximum on the eighteenth day At this point the second triple inoculation is given

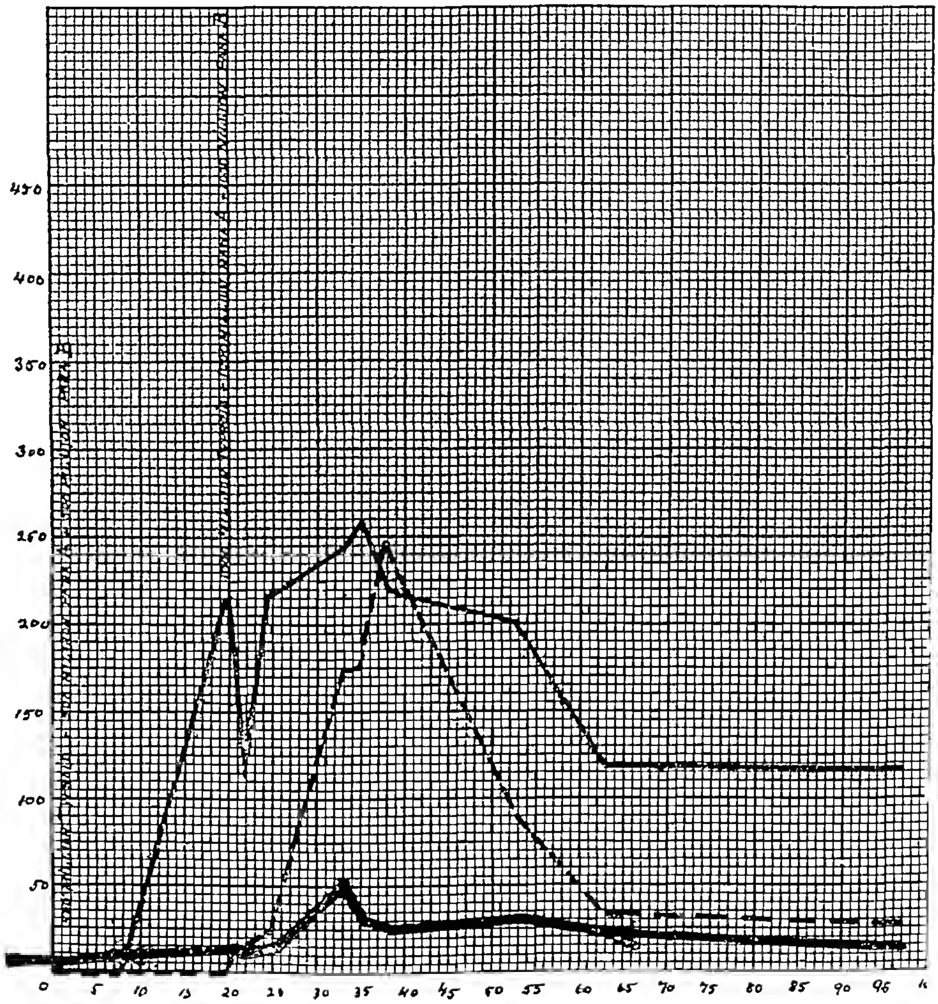
TABLE 26—Data from which Curve 23 Was Plotted

Day of Experiment	Standard Agglutinin Units		
	B Typhosus	B Paratyphosus A	B Paratyphosus B
1	4 3*	0	0
2	Inoculation, 0 5 c c A A	B = 500 million T + 500 m	illion A + 500 million B
8	10 0	1 43	0
20	14 0	214 0	2 85
20	Inoculation, 1 0 c c T A B	= 1,000 million T + 1,000	million A + 1,000 million B
22	13 0	118 0	17 8
25	14 0	219 0	25 0
34	52 0	243 0	173 5
36	29 2	260 0	173 5
39	25 5	218 0	244 0
54	32 4	200 0	89 0
64	21 5	114 2	32 0
97	14 8	114 2	29 0

* Immunized with three doses of B typhosus vaccine (first, 500 million, second, 1,000 million, third, 1,000 million) twenty-five months previous to present experiment

The titer has fallen, that is (negative phase on the second day following this last inoculation), but on the third day the new rise is recorded and on the fourteenth day the maximum is reached A sharp fall (42 per cent) is recorded by the sixteenth day From this point the fall in titer is but gradual, showing that the *T* curve has reached its point of equilibrium

The paratyphoid A agglutinins show a very slight rise on the sixth day following the first triple inoculation This rise reaches its maximum on the eighteenth day At this point the second triple inoculation was given A fall of 45 per cent (that is, negative phase) is recorded two days later and on the



Curve 23

fifth day after the second triple inoculation the new rise occurs, which attains its maximum on the sixteenth day From this point the curve falls, reaching its point of equilibrium on the forty-fourth day after the second triple inoculation When next examined on the seventy-seventh day (after the second triple inoculation) the *A* titer showed no change

The paratyphoid B agglutinins showed a very slight rise on the eighteenth day after the first triple inoculation At this point the second triple inoculation was given The curve continues its rise to a maximum on the nineteenth day after the second triple inoculation From this point the curve falls, reaching its point of equilibrium on the forty-fourth day after the second inoculation The fall noted on the seventy-seventh day was but slight (10 per cent)

DISCUSSION OF RESULTS

In discussing the results obtained in the foregoing experiments it will be of advantage to consider, first, the meaning of the curves obtained in rabbits, together with certain features which are common to both series of curves The curves from man may then be analyzed in the light of the facts observed and the conclusions drawn from the animal experiments

It may, however, be asserted at the outset that both sets of curves exhibit certain points with equal clearness These common general features are the following

1 The general type of the reaction to inoculation is the same throughout both series of curves, the second inoculation with any given vaccine almost invariably raising the agglutinin titer to a much higher level than that reached after the first inoculation And it will be noted that even where the reaction to the first inoculation is somewhat feeble, a good immunity may be expected after reinoculation

2 Individual idiosyncracy plays an important part in the degree of immunity resulting from inoculations made with equal doses of vaccine in different animals of the same species, whatever the particular vaccine employed It also plays a part in determining in mixed inoculation (mixed vaccine) which of the constituent micro-organisms will produce the best reaction

3 Species also clearly plays a part in this connection For it will be noted that while the reaction to paratyphoid B is practically always lowest in the rabbit curves, this is not by any means the case in man

4 The immediate effect of any second immunizing inoculation depends to a considerable extent on the precise period in the curve of the first inoculation at which it is introduced Thus, if the second inoculation is given before the rise due to the first inoculation has reached its maximum, the curve may show no break in continuity, but continues to rise to the maximum resulting from the second inoculation Whether or not a distinct maximum for each rise is seen appears to depend on various factors, one of which is the interval between the two inoculations, and one of three conditions may result (1) the maximum of the first rise may be attained before the second inoculation, (2) the maximum of the first rise may be attained after the second inoculation, in which case a fall will be recorded before the second rise commences, (3) there may, as already stated, be no break in the continuity of the curve, and but one maximum may be noted, which may perhaps represent that of the second rise, or perhaps that of the two rises together

5 These curves have been plotted directly from the actual readings and no attempt has been made to remove any gross irregularities in

TABLE 27—Summary of Tl

Title of Experiment	Bacilli	First Inoculation: Doses*	First Inoculation: First Indication of Rise	First Inoculation: Maximum Rise	Second Inoculation: Interval, Days	Second Inoculation: Doses	Second Inoculation: First Indication of Rise	Ma m R
Group I Curve 1 Rabbit 1	T	1,000	3	9	11	2,000	3	
	A	500	2	6	11	1,000	2	
	B	500	3	6	11	1,000	3	1
Group I Curve 2 Rabbit 2	T	1 000	3	7	15	2,000	1	
	A	500	3	7	15	1,000	2	
	B	500	4	7	15	1,000	3	
Group II Curve 3 Rabbit 3	T	None	0	0		None	0	
	A	500	2	8	11	1,000	3	
	B	500	3	8	11	1,000	3	
Group II Curve 4 Rabbit 4	T	None	0	0		None	0	
	A	500	3	5	11	1,000	1	
	B	500	3	6	11	1,000	1	
Group III Curve 5 Rabbit 5	T	1,000	3	11	11	2,000	4	
	A	None	5	11		None	0	
	B	None	4	5		None	1	[illegible]
Group III Curve 6 Rabbit 6	T	1,000	3	9	11	2,000		
	A	None	0	0		None		
	B	None	0	0		None		
Graup IV Curve 7 Rabbit 7	T	1,000	3	9(12)	9	2,000	1 or 4	13
	A	500	2	8	9	1,000	1	9 or
	B	500	3	9	9	1,000	1	13
Graup IV Curve 8 Rabbit 8	T	1,000	0	0	9	2,000	3	18
	A	500	0	0	9	1,000	3	10
	B	500	0	0	9	1,000	3	10
Group V Curve 9 Rabbit 9	T	500	4	10				
	A	250	2	2				
	B	250						
Group V Curve 10 Rabbit 10	T	500	7	12				
	A	250						
	B	250	17	34				

* Numbers in columns of doses refer to numbers of millions of bacilli injected

—Experiments on Rabbits

Third Inoculation				Fourth Inoculation			
Interval, Days	Doses	First Indication of Rise	Maximum Rise	Interval, Days	Doses	First Indication of Rise	Maximum Rise
55	1,000	4	5	10	2,000	3	6
	None	2	2 and 8		None	0	0
	None	2	9		None	2	2
55	1,000	3	6	10	2,000	3	5
	None	1	2		None	2	3
	None	0	0		None	2	5
	None	0	0		None	5	8
55	500	2	4	10	500	3	7
55	500	3	4	10	500	3	5

TABLE 28—SUMMARY OF RESULTS OF—

Title of Experiment	Bacilli	First Inoculation			Second Inoculation			
		Doses*	First Indication of Rise	Maximum Rise	Interval, Days	Doses	First Indication of Rise	Maximum Rise
Group VI Curve 11 W G	T	500	7	9	9	1,000	5	7
	A	250	7	9	9	500	5	14
	B	250	9	9	9	500	5	14
Group VI Curve 12 J G J	T	500	7	15	15	1,000	7	7
	A	250	7	15	15	500	7	7
	B	250	15	15	15	500	7	7
Group VII Curve 13 R F D R	T	None	0	0		None	0	0
	A	250	7	10 or 14	10	500	9	9
	B	250	7	10 or 14	10	500	4 or 14	16
Group VII Curve 14 H W T	T	None	0	0		None	0	0
	A	250	7	10 or 18	10	500	16	16
	B	250	10	10 or 18	10	500	16	16
Group VIII Curve 15 T P	T	500	7	10	10	1,000	7	7 or 16
	A	None	0	0		None	0	0
	B	None	0	0		None	0	0
Group VIII Curve 16 E A W	T	500	7	10 or 14	10	1,000	4 or 14	14
	A	None	7	10		None		
	B	None	7	10		None	9	9
Group IX Curve 17 W C C	T	500	8	14	19	1,000	38	38
	A	250	8	14	19	500	38	38
	B	250	8	19	19	500	38	38
Group IX Curve 18 F H H	T	500	18	18	21	1,000	23	23
	A	250	18	18	21	500	10	10
	B	250	18	21	21	500	10	10

* Refer to footnote to Table 27

—Experiments on Men

Third Inoculation				Fourth Inoculation			
Interval, Days	Doses	First Indica tion of Rise	Maxi mum Rise	Interval, Days	Doses	First Indica tion of Rise	Maxi mum Rise
23	500			9	1,000	3	12
	None	2	2		None	12	12
	None	2	2		None	12	12
25	500	10	10	10	1,000	2	13
	None	3	3		None	2	2
	None	10	10		None		
	None				None	3	
23	250	5	9 or 12	9	500	3 or 14	3 or 14
23	250			9	500	14	14
	None				None		
25	250	10	10	10	500	2	12
25	250	10	10	10	500	2	12

TABLE 29—SUMMARY OF EXPERIMENTS ON MEN

Title of Experiment	Bacilli	Previous Typhoid Immunization, Doses at Weekly Intervals	First Triple Inoculation				Second Triple Inoculation			
			Interval, Mo	Dose	First Indication of Rise	Maximum Rise	Interval, Mo	Dose	First Indication of Rise	Maximum Rise
Group X Curve 19 J W	T	(1) 500 (2) 1,000	10	500	5	19	19	1,000	14	14
	A	None	10	250	14	19	19	500	14	14
	B	None	10	250	14	19	19	500	14	14
Group X Curve 20 E H N	T	(1) 500 (2) 1,000 (3) 1,000	32	500	3	40	40	1,000	17	17
	A	None	32	250		40	40	500	1	17
	B	None	32	250		40	40	500	1	17
Group X Curve 21 E F H	T	(1) 500 (2) 1,000 (3) 1,000	22	500			9	1,000	5	5
	A	None	22	250	9	9	9	500	5	12
	B	None	22	250	9	9	9	500	5	5
Group XI Curve 22 A D G	T	(1) 1,000	14	500	6	16	16	1,000	7	7
	A	None	14	500	6	16	16	1,000	7	16
	B	None	14	500	16	16	16	1,000	7	18
Group XI Curve 23 C D	T	(1) 500 (2) 1,000 (3) 1,000	25	500	6	18	18	1,000	5	14
	A	None	25	500	6	18	18	1,000	5	16
	B	None	25	500	18	18	18	1,000	2	19

accordance with preconceived ideas as to the form of the finished curves Further experiments are necessary before it is possible to decide whether some of these gross irregularities are due to inaccuracies of technic, or whether they represent the correct amounts of free agglutinins in the circulation at the time of examination

The majority of these irregularities fall into one class, namely, quick secondary rises or rebounds during an otherwise rapidly falling curve (usually thirteen or fourteen days after inoculation) If this sudden secondary rise for from twenty-four to forty-eight hours in a falling curve is not due to faulty technic, it might be explained as the irregular reaction of an exhausted agglutinogenic mechanism The remainder of the gross irregularities occur as sudden, temporary secondary falls during a rising curve Possibly the agglutinogenic mechanism which is responding to the stimulation of the vaccine by a rapid production of free agglutinins into the peripheral circulation is tem-

porarily exhausted and cannot continue its rapid production of agglutinins until after an interval of comparative recuperation or until the mechanism has become compensated or accommodated to this unaccustomed stimulation

As I said before, further experimentation alone will show whether these gross irregularities correctly represent the amounts of free circulating agglutinins at the time of examination, or whether they are due to inaccuracies of technic

The Curves from Rabbits—1 From the Rabbit Curves 3, 4, 5 and 6, it is seen that an animal already immunized to one or more bacilli responds to subsequent inoculations of one or more different bacilli in two ways First, it produces specific agglutinins for the bacilli last injected and second, it shows a temporary new increase in the agglutinin titer for the bacilli injected first Such temporary rises of the original agglutinins exhibit two different types in different cases There may be (1) a sharp "kick-up" following almost immediately on heterologous inoculation (also seen in Curve 13 [human]), or (2) a later rise whose apex corresponds with the maximum of the specific curve of the later immunization The first type is apparently a rapid nonspecific response to the injection of a toxic substance, for an exactly similar reaction has been shown to occur to other forms of chemical or physical irritation (that is, bleeding,[31] injection of any toxic fluid, etc) As I shall point out later (in connection with the Human Curve 13), this sudden increase in agglutinin may perhaps be related to the extensive destruction of leukocytes which Bull[32] states to be caused by inoculations

The latter type of rise may be explained as due to a "sympathetic" increase of activity of the whole antibody producing mechanism at the time when the new specific mechanism reaches its maximum of activity

This "sympathetic" response is also frequently well marked in a somewhat different connection Thus, it may be seen, for instance, in Curve 1, that the typhoid and paratyphoid A curves, following triple inoculation, attain their maxima and commence their fall while the paratyphoid B titer is still rising But as the paratyphoid B curve approaches and attains its maximum, the fall of the typhoid and paratyphoid B curves is arrested, so that a plateau results which persists in each case until after the paratyphoid B titer has passed its maximum

2 By comparing the Curves 3, 4, 5 and 6 with Curves 1, 2, 7 and 8, in which typhoid, paratyphoid A and paratyphoid B were injected simultaneously, it is seen that a given dose of a bacillus when injected *simultaneously* with other bacilli gives rise to as good an immunity

31 Schroeder, K Thesis, Copenhagen, 1906
32 Bull, C G Jour Exper Med, 1916, **23**, 419

reaction as when it is injected alone in the same dosage This point is one of great practical importance in its bearing on prophylactic inoculation against the enteric fevers (typhoid, paratyphoid A, and paratyphoid B)

3 In the Curves 1-8, the commencement of the rise of the agglutinins of the organism first injected shows marked regularity, for in 12 out of 17 instances the rise commenced on the third day, and of the other 5 cases, in 2 it occurred on the second day, in 2 on the fourth and in 1 on the fifth day after inoculation [33]

4 The maxima of the rises in the rabbits' curves due to the first inoculations do not show the same regularity, as they range from the fifth to the eleventh day, the average being 7 7 days

This fact, that is, that the first rise reaches its maximum about the seventh day, is of practical importance, as it indicates the optimum time to give a second inoculation For it is seen that in curves in which the second inoculation is given before the curve from the previous inoculation has commenced to fall, a greater amount of agglutinins is produced

5 For inoculations other than the first there is not the same regularity seen in regard to the commencement of the rise or the attainment of the maximum, though the response is usually more rapid than on the first occasion

6 With the exception of Curves 1, 2, 3 and 5 in rabbits, and 12, 16 and 20 in man, the paratyphoid B agglutinins commence their rise and attain their maximum later than the typhoid and paratyphoid A agglutinins

7 It is evident from the study of Curves 9 and 10, and from a comparison of them with any of the others, that giving a rabbit an inoculation with this dose, that is, 500 million typhoid and 250 million paratyphoid A and 250 million paratyphoid B, produces a much smaller amount of agglutinins than giving a man the same dose, in other words, the mechanism for antibody production in man is very much more sensitive to those organisms than that of a rabbit, and to get similar effects we must increase the dosage for rabbits

This dose of 500 million typhoid and 250 million paratyphoid A and 250 million paratyphoid B is evidently less than the dose required to give a good immunity reaction in rabbits, while a dose of 1,000 million typhoid and 500 million paratyphoid A and 500 million para-

33 It must be remembered in this connection that owing to the exigencies of the case, inoculations could not always be made, or blood withdrawn at a constant hour of the day This was usually done But it is possible that variations in the time of commencement of the rise, not exceeding one day, might be due to early or late inoculation or bleeding as the case may be

typhoid B (as in Curves 1-8) appears sufficient Castellani has shown in rabbits that increasing the dose above this last named strength does not appreciably increase the amount of the agglutinins produced In men in Curves 24 and 25 I found that increasing the proportions of paratyphoid A and paratyphoid B appeared to increase the amount of agglutinins produced for these organisms (in comparison with typhoid titer), but this may have been due to individual idiosyncrasy

The Curves from Man—1 Curves 13, 14, 15 and 16 in the men (as does Curve 3 in rabbits) show that the immunity reaction to the later organism is less intense than that to the first (except for paratyphoid A in curve 16) and may actually fail to reach the level to which the first agglutinins have fallen (B, Curve 15)

Curves 13 and 14 also show that the stimulus of the second immunization causes a definite rise in the agglutinins of the first organisms In Curve 13 the phenomena occurs twice

First within forty-eight hours of the first typhoid inoculation there is a sharp rise of the paratyphoid A and paratyphoid B curves, probably due to the general stimulation of the inoculation already referred to in the discussion of the results in rabbits Since Bull[32] declares that the inoculations cause extensive destruction of leukocytes, it may be suggested that the two phenomena bear a direct relationship to one another and that this leukocytic disintegration liberates the agglutinins, as has been shown in vitro [34]

Secondly, in Curves 13, 14 and 15 a rise in the agglutinins of the first organisms is seen at or about the point at which the maximum of the agglutinins of the later organisms has occurred This second type of rise is of great importance in interpreting the results of clinical agglutination tests in inoculated individuals For instance, in a typhoid inoculated person who acquires a paratyphoid infection, the rise in the typhoid titer which has been described as occurring during the course of the active infection is a rise of this second type The first type of rise (Curve 13) corresponds very closely with the phenomenon seen in the curves of inoculated individuals who have been subjected to a rather intense nonspecific stimulus such as a simple bleeding or the inoculation of an entirely different organism [31]

2 In Curve 16 a plateau is seen in the curve of the organism first inoculated (that is, typhoid) to follow immediately on the first inoculation of the later organisms, that is, paratyphoid A and paratyphoid B I should be inclined to attribute this to the stimulus of this inoculation if it were not for the fact that such plateaus are found to occur in this and in other falling curves at points where no inoculations were given

34 See Footnotes 19, 20 and 21

(*vide supra*) No rise in the typhoid titer is seen at the maximum of the paratyphoid A or paratyphoid B curves, although its apparent absence may be due to the length of the interval between examinations Since it must always be remembered in curves plotted from observations made at intervals longer than twenty-four hours, sharp rises and falls may at times escape detection

3 By comparing Curves 13, 14, 15 and 16 with curves 11 and 12, in which typhoid, paratyphoid A and paratyphoid B were injected simultaneously, it is evident that, as in rabbits, so also in men, the same quantities of bacilli when injected *simultaneously* with other bacilli give for *each* organism *as good* and usually a *greater* immunity reaction than if it had been *injected alone* (and as a first inoculation)

4 In Curves 19, 20, 22 and 23 in which typhoid inoculation had been given from one to three years previously, it was found that when the triple vaccine was injected the typhoid titer rose earlier than in individuals who had not received typhoid injections previously

From this quick response to reinoculation by an immunized individual it may well be deduced that one of the ways in which prophylactic inoculation confers immunity is by habituating the protective mechanism to the formation of particular antibodies so that it remains in a state of readiness which enables it to react with a much shorter latent period to the invasion of the specific organisms and either to prevent them gaining a foothold or to abort the infection in an early stage

5 *Negative Phase*—In certain curves, 14, 15, 16, 18, 19, 20 and 23, in the men, we see (as in Curves 1-6 in rabbits) a short, sharp, unexpected fall within forty-eight hours after any inoculation other than the first This is best interpreted as a negative phase In some cases (that is, in falling curves) this fall might be explained as the continuation of the natural fall, but in other cases, that is, those in which the curve immediately preceding this sharp fall was practically level for six months (as in Curve 19) there *appears* no interpretation other than that of Wright's[35] negative phase This would *appear* to be in contradiction to the results of Bull [32]

CONCLUSIONS

From the foregoing discussion of the results obtained in these experiments the following conclusions bearing on the practical problem of prophylactic inoculation in man against the typhoid-paratyphoid group of organisms stand out as possessing paramount importance

1 When a mixed vaccine is used the immunity obtained for each of its constituent bacilli is at least as good as, and very often greater

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35 Wright, A E Brit Med Jour, 1903, **1**, 1069 Von Wassermann, A, and Summerfield, P Med Klin, 1915, **11**, 1307

than, that obtained against any one of these organisms when it is employed alone in the same dosage for a first immunization

2 When single vaccines are employed in succession and the immunizations are carried out independently, the response is greatest to that vaccine which is introduced first To the later immunizations with other micro-organisms the specific response is almost always less intense It has associated with it, however, as a secondary result the production of a new rise of variable extent in the agglutinin titer of the serum of the bacillus of the first immunization

ADDITIONAL REFERENCES

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Madsen and Jorgensen, Festskrift ved Indu af Statans Seruminst, Copenhagen, 1902

A STUDY OF THE METABOLISM OF ASTHMA *

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The effects of asthma on the anabolism and katabolism of the human body should be considered from different points of view The causative factor (for example, anaphylaxis, etc) may induce certain pathochemical changes which lead to asthma as one of the results, and these pathochemical changes are the disturbing factors in the metabolism of these patients, or, again, the syndrome, asthma, may affect the metabolism of the patient by (for instance) depriving the blood of oxygen, or by affecting the nervous system, circulatory system, etc When, therefore, results are reported of the metabolism findings in asthmatic individuals, discrimination should be used as to which factor is to be held responsible for these deviations from the normal chemical balance of the body

Before discussing the experiments that we have performed in our study of this disease, we wish to review the literature that may be pertinent to this subject We have found no report of a complete metabolism study of patients suffering from asthma The effect of dyspnea on metabolism has, however, been investigated

Senator[1] has found that moderate respiratory impediment affects but little the nitrogen katabolism, sometimes augmenting it slightly, whereas if the dyspnea becomes very great, the increase of the nitrogen excretion is marked and may last several days after the disappearance of the dyspnea (Fraenkel,[2] Fleischer and Penzoldt,[3] Fraenkel and Geppert,[4] Klemperer,[5] Praussnitz,[6] Araki[7])

Colosanti is the only observer who comes to the opposite conclúsion, and his reputation is such that his work cannot be slighted Colosanti and Palamenti obstructed the breathing by chemical and by mechanical means, and found that the percentages of urea and nitrogen in the urine were both subnormal as long as the obstruction was main-

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* From the Department of Laboratories, Beth Israel Hospital

1 Senator Arch f path Anat u Physiol, 1868, **42,** 1
2 Frankel Arch f path Anat u Physiol, 1876, **57,** 273
3 Fleischer and Penzoldt Arch f path Anat u Physiol, 1882, **78,** 210
4 Fraenkel and Geppert Ueber die Wirkungen der verdunnten Luft auf den Organ, 1883, p 78
5 Klemperer Ztschr f klin Med, 1889, **16,** 584
6 Praussnitz Sitzungsb d Gesellsch f Morphol u Physiol in Munchen, 1890, **5,** 70
7 Araki Ztschr f physiol Chem, 1891, **15,** 335
8 Colosanti and Palamanti Maly's Jahresb u d Fortschr d Thierchem, 1894, **24,** 466

tained, rising again when the impediment was removed They also say that the secretion of urine ceased during dyspnea

Matthes[9] writes "One must hesitate before accepting unqualifiedly their conclusions that the lessened supply of oxygen diminished the activity of the regressive metamorphoses of the organism"

We shall discuss the Colosanti results later

It has been generally accepted by the German school that there is a breaking down of protein in dyspnea Whether this is due to a breaking down of the body cells due to lack of oxygen (a theory suggested by Frankel), or whether (as Klemperer asserts) the increased protein katabolism is due to a poison produced by the dyspnea, or whether (according to Praussnitz) the primary effect of the dyspnea is to break down the nonnitrogenous substances in the body, and only secondarily to augment the protein decomposition—is a much mooted point

Saccone[10] found that the restriction of respiration in a dog by the application of a Sayre corset caused an increased elimination of urinary phosphorus, which became normal only after two days

It has been found by a number of observers that when tissue oxidation is lessened, due to dyspnea, unoxidized products may be eliminated in the urine, as, for example, lactic acid Senator,[1] for instance, found glucose in the urine of dogs with dyspnea, and Dastre[11] found a hyperglycemia in similar conditions It was proved by Hoppe-Seyler[12] that the lactic acid excreted under these circumstances was paralactic acid, that is, ethylidene lactic acid

Dyspnea may be induced by vagus paralysis But it has been found by Rauber and Voit[13] that the oxygen absorption and the carbon dioxid elimination were not changed in experimental section of both vagi Von Maar,[14] however, reported different results

The absorption of oxygen increases considerably, and generally is doubled, in the lung whose vagus is cut, and it falls almost as much in the other lung The excretion of carbon dioxid was affected in the same sense as the absorption of oxygen, but to a far less extent Von Maar found that as soon as the other vagus was cut, the breathing of the two lungs became equalized He exposed and scrutinized the lung during one experiment, and could see no change in the amount of blood that it contained, thus making it plain that the circulation had nothing to do with the changes observed On the other hand, by compressing the left pulmonary artery, he did directly disturb the circulation through the lungs (Matthes[15])

9 Matthes, M, in C von Noorden's "Metabolism and Practical Medicine," 1907, **2**, 331

10 Saccone Ann di med nav, 1907, **13**, (1), 573

11 Dastre De la Glycemie asphysique, These de Paris, 1879

12 Hoppe-Seyler Ztschr f physiol Chem, 1895, **20**, 365

13 Rauber and Voit Sitzungsb d k Akad d Wssensch, zu Munchen, 1868

14 Von Maar Skand Arch f Physiol, 1902, 229

15 Matthes von Noorden Metabolism and Practical Medicine, 1907, **2**, 304

CASE 1 —*History*—A married woman aged 40, developed a severe attack of asthma when in midocean seven years previously, and continued to be afflicted in varying degrees of severity and almost without interruption until the present report One maternal aunt was an asthmatic As a child the patient had one or two attacks of oppressed breathing History and family history are otherwise negative in so far as they have a bearing on the asthmatic state Her condition at the time of the examination showed a normal blood pressure, and gave normal urinary findings on routine examination There was a profuse expectoration of mucopus containing a great variety of bacteria, and there was considerable mucus in the stool Roentgen-ray examination of the lungs had already shown an absence of any tuberculous lesion, but disclosed the fact that the larger bronchial tube walls were much hypertrophied—a result no doubt of the long continued effort at forced breathing

Preliminary Laboratory Examinations—The urine was light, amber, specific gravity 1 018, acid, containing no albumin, glucose or the acetone derivatives, showing a trace of indican Microscopically, many squamous epithelial cells derived from the vulva were present

Examination of the blood was negative

The feces were yellow in color, of semisolid consistence, containing no blood, but rather excessive quantities of mucus which was microscopically negative

Bacteriologic examination of the sputum showed the presence of staphylococcus, streptococcus, and *Micrococcus catarrhalis*

The Wassermann test was negative (Dr Bronfenbrenner)

Method of Procedure—The patient was put on a Folin diet, which consists of

Whole milk, 500 c c
Cream (18-22 per cent fat), 300 c c
Eggs (white and yolk), 450 gm
Horlick's malted milk, 200 gm
Sugar, 20 gm
Sodium chlorid, 6 gm
Water enough to make the whole up to 2 liters

"The ingredients combine into a liquid mixture containing 119 gm protein, and approximately 148 gm fat and 225 gm carbohydrates" (Folin)

The patient was kept on this diet for three days The twenty-four-hour urine collections were preserved with thymol The daily intestinal evacuations were marked off by a capsule of carmin (0 3 gm)

The following methods were used for the analyses of the urine and feces The nitrogen was estimated according to Kjeldahl, and the total sulphur by the Benedict[16] method, total and ethereal sulphates, by the Folin[17] method, the inorganic sulphates were computed by subtracting the ethereal sulphates from the total sulphates, the "neutral" sulphur was computed by subtracting the total sulphate sulphur from the total sulphur Urea was estimated by Benedict's[18] method ammonia and creatinin by Folin's[19] methods, uric acid by the Folin-Shaffer[20] method, purin bases by the Kruger-Schmidt[21] method, phosphorus by Neumann's[22] method, calcium and magnesium by McCrudden's[23] method

16 Benedict Jour Biol Chem, 1909, **6,** 363
17 Folin Am Jour Physiol, 1905, **13,** 51
18 Benedict Jour Biol Chem, 1911, **8,** 455
19 Folin Am Jour Physiol, 1903, **8,** 330
20 Folin and Shaffer Ztschr f physiol Chem, 1901, **32,** 552
21 Kruger and Schmidt See Hawk, Practical Physiol Chem, Ed 5, 1916, 513
22 Neumann Ztschr f physiol Chem, 1904, **43,** 45
23 McCrudden Jour Biol Chem, 1911, **10,** 187

METABOLISM STUDIES

Study of the Nitrogen Metabolism—The patient took in daily an average of 17 5 gm nitrogen in her food In the urine she voided daily an average of 11 4 gm nitrogen, and in her feces, an average of 2 2 gm nitrogen There was thus left a positive balance of 3 9 gm Nitrogen representing 33 15 gm protein

The nitrogen partition of the urine shows the following The percentage excretion of urea, ammonia, and uric acid nitrogen is normal There is a slight increase in the elimination of the creatinin and amino-acid nitrogen The data for the nitrogen partitions are represented in Table 1

Study of the Sulphur Metabolism—The patient took daily in her food an average of 3 2 gm sulphur trioxid (SO_3) and voided in the urine daily an average of 2 4 gm sulphur trioxid, and in the feces 0 93 gm, causing a negative balance of 0 13 gm It thus seems that in this case the katabolism of the sulphur portion of the molecule does not go hand in hand with the nitrogen katabolism, for, whereas there was a positive average balance of 3 9 gm nitrogen, the sulphur shows a loss The sulphur partition in the urine is very interesting There is an increase in the nonoxidized sulphur fraction (so-called "neutral sulphur") This would be in harmony with the findings of Reale and Boeri,[24] who observed that by inducing dyspnea in dogs by compression of the chest, there was a marked increase in the "neutral" sulphur fraction of the urine — even as high as 37 5 per cent of the total sulphur

The ethereal sulphates were not increased, showing that there was not present to any extent an intestinal putrefactive condition Von Noorden[25] found, in general, that there was no deviation from the normal in the limination of the conjugated sulphates in the urine by emphysematous subjects

Since one of us is interested in the volatile sulphids eliminated in the urine, we determined that fraction in the urine was found that from 2 to 3 per cent of the total sulphur was volatile sulphid We made no attempt to identify which of the volatile sulphids were present It would be interesting to analyze such urine for hydrogen sulphid, mercaptan, ethylsulphid, etc

The ratio of nitrogen to sulphur was on the average of 11 5 1 The data of the sulphur partition are given in Table 2

Study of the Mineral Metabolism — As will be seen from the accompanying data on Table 3, there was nothing strikingly abnormal

24 Reale and Boeri Wien med Wchnschr, 1895
25 Von Noorden See Matthes, Footnote 15

TABLE 1—NITROGEN PARTITION—

Day	Volume Urine, C c	Nitrogen Gm	Urea N		Ammonia N	
			Per Cent Total N	Gm	Per Cent Total N	Gm
1	1,070	12 3	82 7	10 1721	2 5	0 3074
2	760	10 4	80 5	8 373	2 2	0 2288
3	890	11 7	80 2	9 385	3 9	0 4563
Average	906	11 4	81 1	9 2455	2 8	0 3192

TABLE 2—SULPHUR PARTITION OF URINE, CASE 1

Day	Total S as SO_3, Gm	Inorganic SO_3		Ethereal SO_3		Neutral S as SO_3			N S Ratio
		Per Cent Total SO_3	Gm	Per Cent Total SO_3	Gm	Per Cent Total SO_3	Gm	Volatile S Portion, per Cent of Total SO_3	
1	2 7	68 8	1 8576	12 8	0 3456	18 4	0 4968	2 4	11 3 1
2	2 1	67 4	1 4254	14 9	0 3129	17 7	0 3727	2 35	12 2 1
3	2 6	66 7	1 7342	14 2	0 3692	19 1	0 4986	2 97	11 2 1
Aver	2 4	67 6	1 6224	13 9	0 3336	18 4	0 4416	2 57	11 5 1

TABLE 3—MINERAL EXCRETION IN THE URINE AND FECES, CASE 1

Day	Phosphorus Pentoxid		Calcium Oxid		Magnesium Oxid		Chlorin in Urine, Gm
	Urine, Gm	Feces, Gm	Urine, Gm	Feces, Gm	Urine, Gm	Feces, Gm	
1	2 9	1 2	0 6	1 61	0 92	0 57	5 7
2	3 1	0 8	0 67	1 59	0 87	0 32	5 2
3	2 7	1 9	0 72	1 82	0 91	0 42	6 3
Average	2 9	1 3	0 66	1 67	0 9	0 43	5 7
Total	4 2		2 33		1 33		

in the elimination of phosphorus, calcium and magnesium in the urine and feces There was an average daily positive balance of 0 9 gm phosphorus pentoxid (P_2O_5), 0 36 gm calcium oxid (CaO), 0 12 gm magnesium oxid (MgO) The French school of physicians have described phenomena of marked demineralization, that is, loss of calcium oxid, phosphorus pentoxid and magnesium oxid in pulmonary

—OF URINE CASE 1

Amino Acid N		Uric Acid N		Purin Base N		Creatinin N		Rest N
Per Cent Total N	Gm	Per Cent Total N	Gm	Per Cent Total N	Gm	Per Cent Total N	Gm	Per Cent Total N
2 1	0 2583	2 7	0 3321	2 2	0 2706	5 7	0 7011	0 2
3 7	0 3848	1 8	0 1871	2 1	0 2184	6 1	0 6344	3 3
4 3	0 5031	2 8	0 3276	1 9	0 2223	5 8	0 6786	1 1
3 3	0 3762	2 4	0 2736	2 06	0 2348	5 6	0 6612	1 5

TABLE 4—BALANCE SHEET, CASE 1

	Nitrogen		Sulphur Trioxid		Phosphorus Pentoxid		Calcium Oxid		Magnesium Oxid	
	Feces, Gm	Urine, Gm	Feces, Gm	Urine, Gm	Feces, Gm	Urine, Gm	Feces, Gm	Urine, Gm	Feces, Gm	Urine, Gm
Aver daily intake	17 5		3 2		5 1		2 7		1 4	
Output first day	12 3	2 2	2 7	0 8	2 9	1 2	0 6	1 61	0 92	0 57
Total	14 5		3 5		4 1		2 21		1 49	
Output second day	10 4	2 7	2 1	0 7	3 1	0 8	0 67	1 59	0 87	0 32
Total	13 1		2 8		3 9		2 26		1 19	
Output third day	11 7	1 8	2 6	1 3	2 7	1 9	0 72	1 82	0 91	0 42
Total	13 5		3 9		4 6		2 54		1 33	
Average output	11 4	2 2	2 4	0 93	2 9	1 3	0 66	1 67	0 9	0 43
Total	13 6		3 33		4 2		2 33		1 33	
Total intake, three days	52 5		9 6		15 3		8 10		4 2	
Total output, three days	41 1		10 2		12 6		7 01		4 01	
Balance after three days	+11 4		—0 6		+2 7		+1 09		+0 19	
Average daily balance	+3 8		—0 2		+0 9		+0 36		+0 12	

phthisis This patient has no evidence whatever of tuberculosis As far as we are aware, the mineral metabolism of asthma has never been previously studied

In Table 4 is given a balance sheet of the intake and output of nitrogen, sulphur trioxid, phosphorus pentoxid, calcium oxid and magnesium oxid The average intake of the three days is given The output data are given in their daily quantities

CASE 2—*History*—A young woman, aged 29, married, with a healthy child Her family history is negative Her past history shows that when a child she had several attacks of pleurisy and pneumonia During the past few years she complains of shortness of breath, of occasional typical asthmatic seizures, which pass off after several hours Her heart and kidneys are normal A slight degree of emphysema is present

The urine examination is negative, specific gravity, 1 016 Examination of the feces is negative The sputum shows many streptococci, pneumococci and pus cells Negative for tubercle bacilli after guinea-pig inoculation The blood count shows hemoglobin, 90 per cent , red blood cells, 4,200,000, white blood cells, 10,200, polynuclears, 62 per cent , mononuclears, 35 per cent , eosinophils, 3 0 per cent The Wassermann test is negative

This patient was also kept on a Folin diet for three days, and her metabolism was studied on the plan described under Case 1

Study of the Nitrogen Metabolism—From the data of Table 8 it will be seen that the patient took in daily an average of 18 8 gm of

TABLE 5—URINARY NITROGE

Day	Volume Urine, C c	Nitrogen	Urea N		Ammonia N	
			Per Cent Total N	Gm	Per Cent Total N	Gm
1	1,520	14 94	85 5	12 7737	4 7	0 7022
2	1,725	14 82	86 4	12 805	4 1	0 6076
3	1,650	14 35	84 2	12 1827	3 5	0 5022
Average	1,631	14 703	85 3	12 5391	4 1	0 6027

TABLE 6—URINARY SULPHUR PARTITION, CASE 2

Day	Total S as SO_3, Gm	Inorganic SO_3		Ethereal SO_3		Neutral S as SO_3			N S Ratio
		Per Cent Total SO_3	Gm	Per Cent Total SO_3	Gm	Per Cent Total SO_3	Gm	Volatile S Portion, per Cent of Total SO_3	
1	3 87	52 4	2 0278	29 7	1 1494	17 9	0 6917	2 15	9 9 1
2	3 81	54 1	2 0558	26 8	1 1211	19 1	0 5677	3 22	9 5 1
3	3 72	56 0	2 0832	27 5	0 8230	16 5	0 6138	2 17	9 8 1
Aver	3 8	54 1	2 0558	28 0	1 0640	17 8	0 6764	2 51	9 7 1

TABLE 7—MINERAL EXCRETION IN URINE AND FECES, CASE 2

Day	Phosphorus Pentoxid		Calcium Oxid		Magnesium Oxid	
	Urine, Gm	Feces, Gm	Urine, Gm	Feces, Gm	Urine, Gm	Feces, Gm
1	3 21	1 07	0 92	2 2	0 35	0 09
2	3 32	1 12	0 85	2 5	0 32	0 11
3	2 95	1 70	0 94	2 4	0 33	0 12
Average	3 19	1 29	0 903	2 3	0 33	0 106
Total	4 48		3 203		0 436	

nitrogen and excreted daily an average of 14 703 gm nitrogen in the urine and 2 83 gm in the feces showing a positive average balance of 1 267 gm nitrogen, or 7 918 gm protein The nitrogen partition was normal, except perhaps that there is a slight deduction in the creatinin excretion The urea nitrogen, ammonia nitrogen purin base and uric acid nitrogen and amino-acid nitrogen fractions are normal

Study of the Sulphur Metabolism—It will be seen (Table 8) that the patient took in a daily average of 4 785 gm sulphur trioxid in her

—Partition, Case 2

Amino Acid N		Uric Acid N		Purin Base N		Creatinin N		Rest N
Per Cent Total N	Gm	Per Cent Total N	Gm	Per Cent Total N	Gm	Per Cent Total N	Gm	Per Cent Total N
1 7	0 2539	2 0	0 2988	2 1	0 3137	2 2	0 3298	1 8
2 1	0 3112	1 9	0 2816	2 5	0 3705	2 7	0 4001	0 4
1 9	0 2726	17	0 2439	1 9	0,2726	3 2	0 4592	2 6
1 9	0 2793	1 86	0 2734	2 1	0 3087	2 7	0 3569	1 6

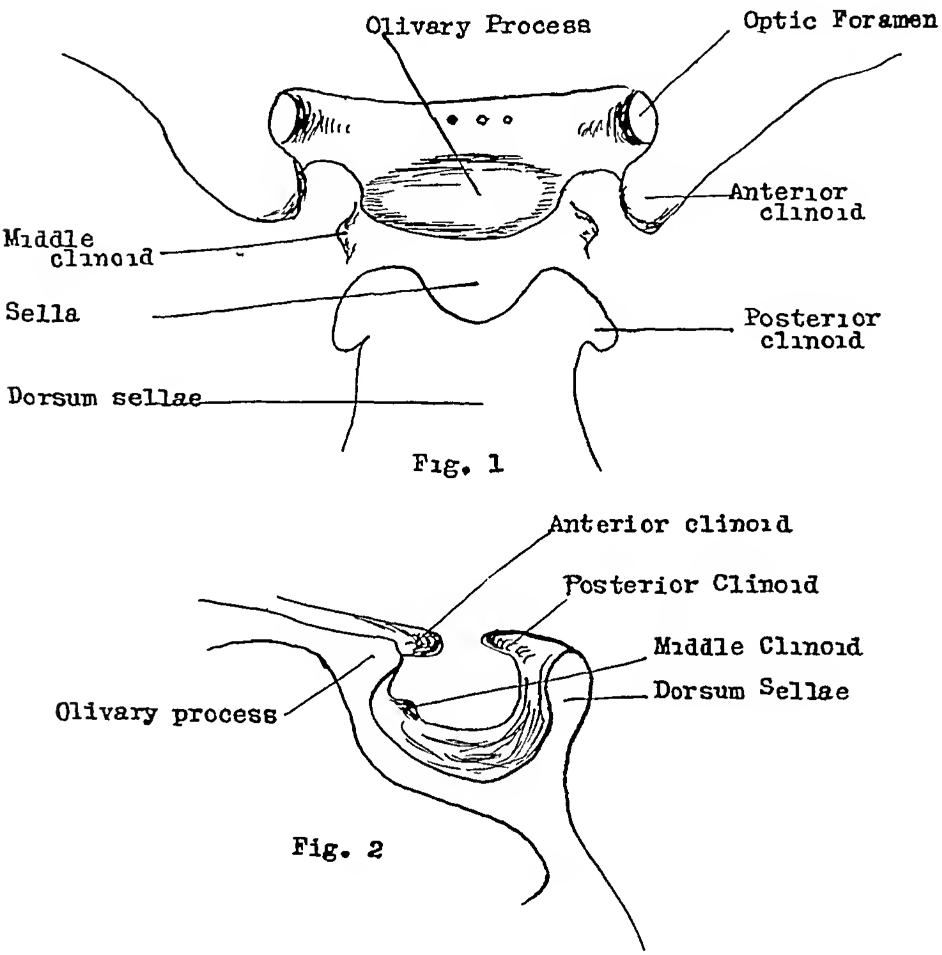
TABLE 8—Balance Sheet Case 2

	Nitrogen		Sulphur Trioxid		Phosphorus Pentoxid		Calcium Oxid		Magnesium Oxid		Chlorin in Urine, Gm
	Urine, Gm	Feces, Gm	Urine, Gm	Feces, Gm	Urine, Gm	Feces, Gm	Urine, Gm	Feces, Gm	Urine, Gm	Feces, Gm	
Aver daily intake	18 8		4 785		4 91		3 25		0 46		6 37
Output first day	14 94	2 37	3 87	0 65	3 21	1 07	0 92	2 2	0 35	0 09	6 14
Total	17 31		4 52		4 28		3 12		0 44		
Output second day	14 82	2 56	3 81	0 67	3 32	1 12	0 85	2 5	0 32	0 11	6 25
Total	17 38		4 48		4 44		3 35		0 43		
Output third day	14 35	2 74	3 72	0 72	2 95	1 70	0 94	2 4	0 33	0 12	6 03
Total	17 09		4 44		4 65		3 34		0 45		
Average output	14 703	2 83	3 8	0 68	3 19	1 29	0 903	2 3	0 33	0 106	6 14
Total	17 533		4 48		4 48		3 203		0 436		
Total intake, three days	56 4		14 355		14 73		9 75		1 38		
Total output, three days	52 599		13 44		13 44		9 609		1 308		
Balance after three days	−3 601		−0 915		+1 29		+0 141		−0 072		
Average daily balance	−1 267		−0 305		−0 43		−0 047		+0 024		

food, and that she eliminated a daily average of 3 8 gm sulphur trioxid in the urine and 0 68 gm sulphur trioxid in the feces, leaving a daily positive balance of 0 305 gm sulphur trioxid

The urinary sulphur partition (Table 6) is interesting The excretion of ethereal sulphates is increased the figures being almost twice

finally the shape of the parts was recorded by tracing their outlines on glass, with pen and drawing ink Two tracings were made, one by placing the glass flat on the base of the skull over the pituitary (corresponding to Figure 1), and the other by tracing the outline of the surface of the bone, after a sagittal saw cut in the median plane had permitted chipping away one side of the region For this a sheet of mica was used because of its thinness and the outline afterward trans-



Figs 1 and 2—Showing conformation of the sellar region Reduced one third

ferred to glass These tracings may be preserved as such, or may be reproduced by contact through photographic processes The material here presented has been collected entirely within the Craig Colony's necropsy service, mostly by myself, but in part by Drs Shaw and Joy, to whom my thanks are due The eighty-five cases presented are very largely consecutive and the omissions and additions from the series are due, with one exception, to reasons of expediency, in other words, this series does not represent selected material

The line of vision of the roentgenologist and of the pathologist are different by 90 degrees The roentgenologist views the sella along a line parallel to that joining the two external auditory meatuses — from the side, in this position the clinoid processes necessarily cast a shadow which seems to be above and across the hollow of the sella, and any increase in their length will give a shadow completely closing

Fig 3—The approximated finger tips used to represent the clinoids

the mouth of the sella The pathologist at necropsy sees these structures from above, along a line at right angles to that of the roentgenologist The sella and its neghborhood are exposed flat to view and the actual relations of the parts can be seen, it will always be found that no matter how the clinoids overlap, they are laterally placed and always have between them an opening over the gland, covered by dura

Fig 4—Representing the opening between the laterally placed clinoids

In Figures 3 and 4 the approximated finger tips are used to represent the clinoids, in Figure 3 the finger tips are seen as the roentgenologist sees the clinoids, while in Figure 4, the large opening between the laterally placed clinoids is well shown

Unfortunately, normal material has not been available to me for use as a standard Through the courtesy of the late Dr Gibson of the

University of Buffalo I was able to obtain some tracings of presumably nonepileptic sellas, shown in Figure 5 It is interesting to note the diversity of these sellas and to comment on the fact that in the normal material seen in the University's bone room, the middle clinoids were practically always distinctly present, while in our epileptic material the middle clinoids were practically always absent

Only selected drawings (Figs 8, 9 and 10) are reproduced with this article, but an inspection of the entire series shows that in the

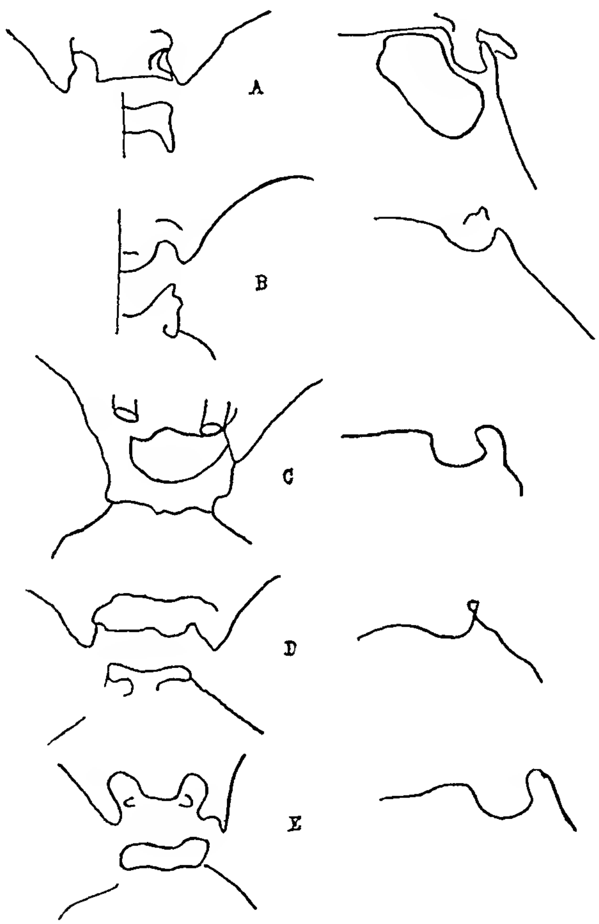


Fig 5—Presumably normal sellas Reduced one half

epileptic there is no constant shape or type of sella, but that, on the contrary, there is a wide diversity This will be shown by various tabulations

TABLE 1—General Conformation

	Cases
Average or large	61
Small	16
Average or normal depth	64
Shallow	13
Deformed	16

From the horizontal tracings we can predict what sort of shadow our cases would have cast on the roentgen ray plate The *inter clinoid gap* is the measure of this and is determined as follows

The tips of the anterior clinoids are joined by a line A line parallel to this is drawn through the most anterior portion of the posterior clinoids, the distance between these two lines is the inter-clinoid gap Since the roentgen rays diverge somewhat, the shadow of the gap will be somewhat wider than the above measure, dependent

Weight mgs.	5mm	6mm	7mm	8mm	9mm	10mm	11mm	12mm	13mm	Total
200mgs		2		1						3
300			1	1	1					3
400		1	1	4	4	2	3	1		16
500				4	1	2	2	1		10
600				1	1	2	4	1	2	11
700					1	2				3
800							1			1
900										
1000mgs										

Fig 6—Relation of pituitary weight to anterior-posterior diameter of sella

on the position of the tube The results of this measurement are as follows

TABLE 2—Interclinoid Gap

	Cases
No gap	34
1 mm or less	10
1 mm up to 2 mm	16
2 mm up to 4 mm	20
4 5 mm up to 6 5 mm	5
Total	85

It must be admitted from this tabulation that roofing would appear in a majority of the cases of this series

Before accepting this as evidence of compression, we must recall that the anatomist always sees an open space above the gland, filled

only by dura and bounded laterally by the clinoids This space is clearly seen in the median sagittal sections, and measuring the narrowest portion of the aperture we have the following

TABLE 3—Effective Opening of Sella

	Cases
5 mm to 6 5 mm	11
7 mm to 10 5 mm	54
11 mm to 13 mm	12
Total	77

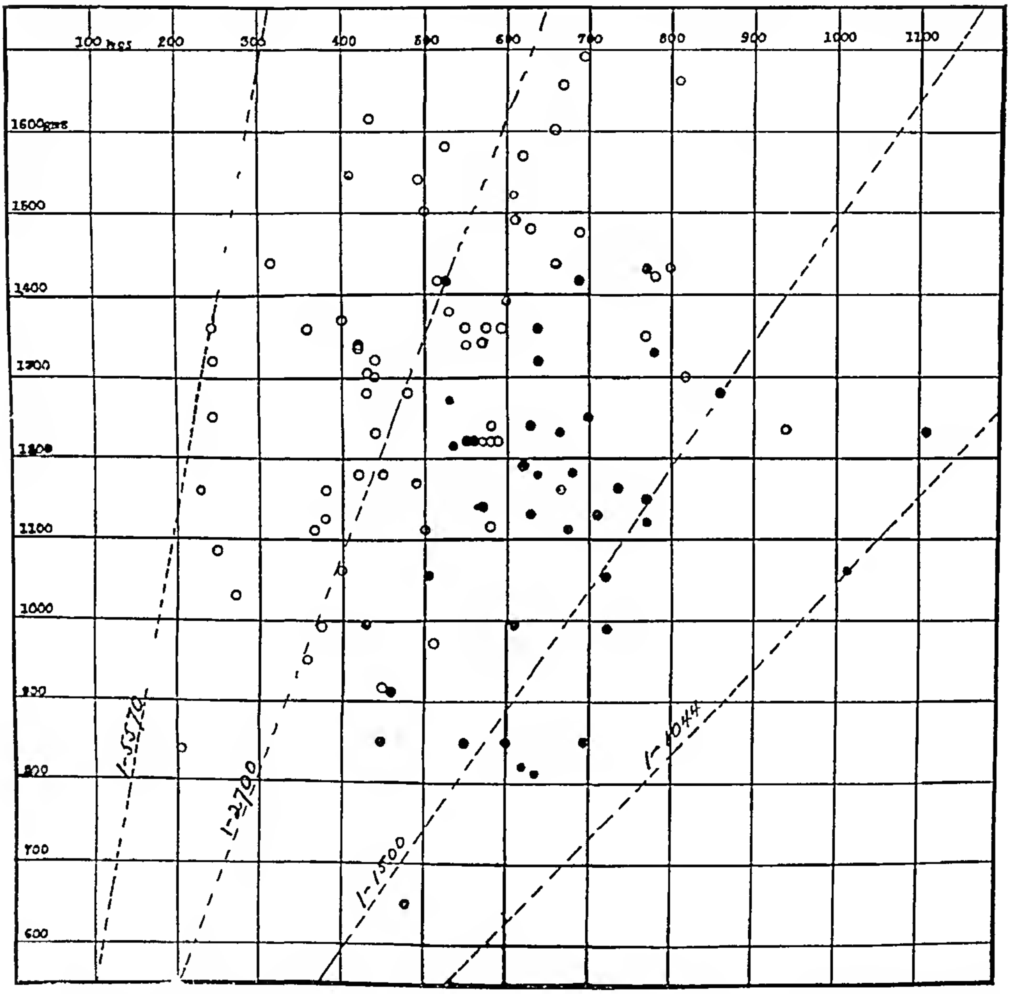


Fig 7—Showing beam weight and pituitary weight for males and females Dotted lines show ratio to one part of pituitary The circles are males, dots females

The sella is bounded anteriorly by the olivary eminence and posteriorly by the dorsum sellae These structures are sometimes so shaped as to narrow the opening of the sella, so that the effective opening is less than the greatest anterior-posterior diameter The relations of these measurements are shown by a comparison of Tables 3 and 4, and the amount of overhang is shown in Table 5

TABLE 4—ANTERIOR-POSTERIOR DIAMETER (GREATEST)

	Cases
5 mm to 7 5 mm	9
8 mm to 11 5 mm	62
12 mm to 13 mm	6
Total	77

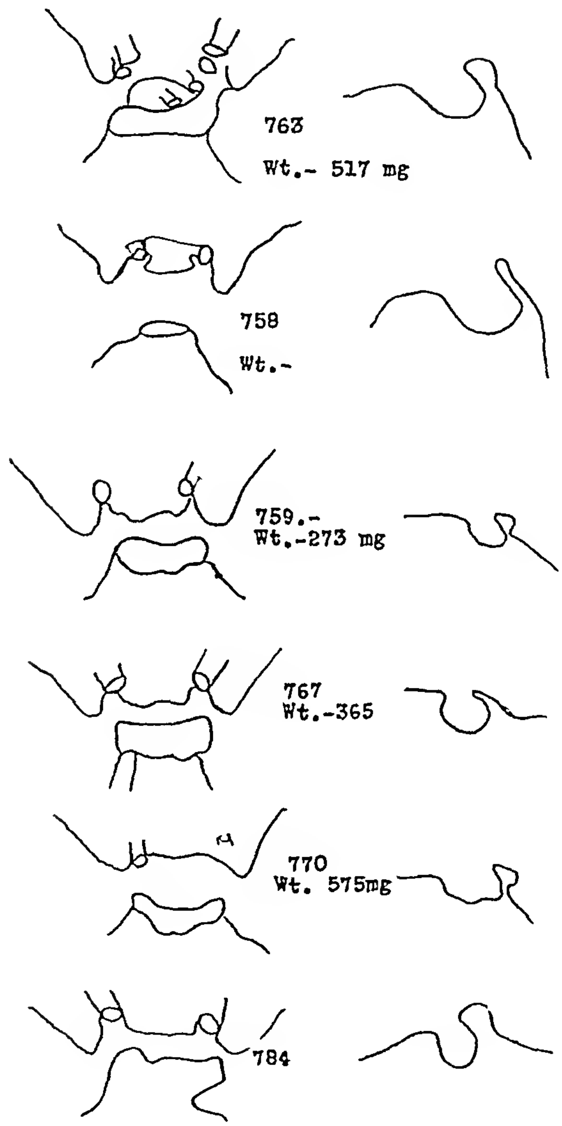


Fig 8—Diagrams showing the diversity in shapes of the sella in different epileptic subjects Reduced one half

TABLE 5—OVERHANG (ANTERO-POSTERIOR DIAMETER GREATER THAN EFFECTIVE OPENING)

	Cases
No overhang	41
Slight (about 1 mm)	18
Some (about 2 mm)	13
Marked (3 to 4 mm)	5
Total	77

In addition to actual overhang, some limitation of the sella is produced by changes in the shape of the olivary eminence This is shown in the anatomic drawing as a rounded prominence, but in many of our cases, its sagittal section shows a sharp angle at the anterior border of the pituitary, and even more important, the olivary eminence becomes possessed of lateral angular processes which tend to encroach on the cavity of the sella

Fig 9—Additional types of sella in epileptics Reduced one half

The sellas have shown considerable variation in depth

TABLE 6—Depth

	Cases
5 mm to 7 5 mm	17
8 5 mm to 9 5 mm	42
10 mm to 12 mm	9
Total	78

For comparison as to the size of the normal sella the following figures may be quoted

TABLE 7—NORMAL MEASUREMENTS

	Antero-Posterior	Transverse	Depth
Keith[5]	10 to 12 mm	14 to 15 mm	8 mm
Dock[6]	6 to 10 5 mm		10 to 14 5 mm
Biedl[6]	14 mm		5 5 mm
Fearnsides[7]	10 to 12 mm		8 mm
	Weight, from 590 mg to 731 mg		

Comparing these figures with those recorded from our series, it would seem that our cases run somewhat smaller than the normals

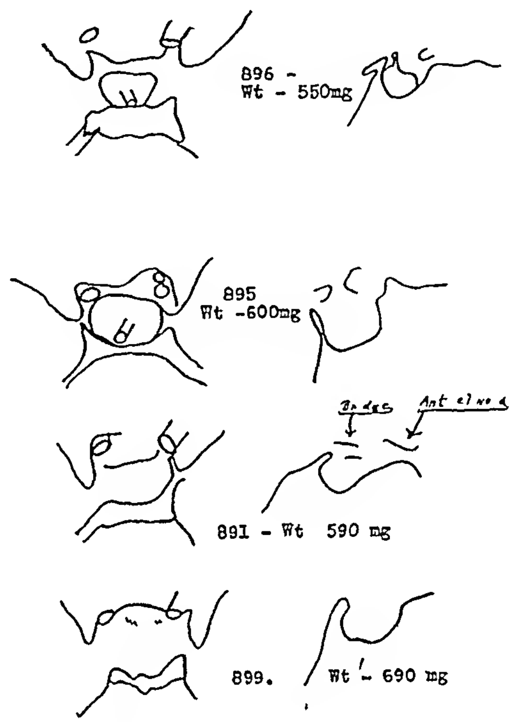


Fig 10—Types of sella in epileptics Reduced about one half

The weights of 116 glands have been recorded and are shown in the following tabulation

TABLE 8—WEIGHTS OF 116 GLANDS

	Cases
Between 200 and 300 mm	8
300 and 400 mm	8
400 and 500 mm	26
500 and 600 mm	28
600 and 700 mm	28
700 and 800 mm	11
800 and 900 mm	4
1,000 to 1,100 mm	3
Total	116

It has been mentioned that the gland is often smaller than the sella in our cases

5 Keith Lancet, London, 1911, **1,** 993
6 Quoted by Munson and Shaw, Footnote 1
7 Fearnsides Lancet, London, 1914, **2,** 16

The relation of anterior-posterior diameter of the sella and the weight of the pituitary has been plotted in a few cases and shows (Fig 6) that the weight of the gland and the diameter of the sella decrease together

Another chart (Fig 7) shows the relation of brain weight to the pituitary weight, by males and females We see that female brains tend to run lighter in weight than the males, but that the female pituitary glands are distinctly heavier than those of the males The ratios of these two weights are widely variable — from 1 part pituitary to 5,570 of brain tissue, to 1 to 1,044 The dashed lines shown in the figures are representative of the ratios indicated, and are drawn from the imaginary zero of the chart

Certain deformities have been noted which may be briefly mentioned

Middle clinoid processes were seen in only two of our cases

The modifications of the olivary eminence by its overhang and by lateral angles have been mentioned

Modifications in the shape of the dorsum sellae are numerous and are shown in the sagittal tracings especially The shed-roof type, the grossly thickened, and the slender delicate represent wide variations of type Notably, the middle of the dorsum sellae is lowered by a deep notch, sometimes extendinging almost to the floor of the sella

The anterior and posterior clinoids not infrequently join each other in bony continuity, thus, five times on the right, once on the left and once both sides were thus joined In addition, bony foramina for the internal jugulars are not uncommon and seem to be formed by bony bands between the anterior clinoids and the region where the middle clinoid should be Spicules are also present in the dura continuous with the posterior clinoids

In seven cases, there was very well marked asymmetry

Once the anterior clinoid showed an exostosis

Bony channels on the posterior surface of the dorsum sellae or extending transversely through it from side to side, and containing blood-channels, are not uncommon

CONCLUSIONS

The sellas from a series of unselected epileptic subjects present a wide variation in type The average size seems a trifle smaller than the figures given for normals and the contained gland seems to weigh less

Roofing will be seen in the roentgenogram, but in reality the gland is well exposed and pressure seems a remote possibility Bony changes are present but seem to be the anomalies which might well be present in a similar series of nonepileptic cases There is no characteristic change to be seen in epileptic sellas

THE INTRAVENOUS SERUM TREATMENT OF EPIDEMIC CEREBROSPINAL MENINGITIS

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Chief of the Medical Service, Base Hospital
CAMP JACKSON, S C

The meningeal aspect of meningococcus infections has usurped such a prominent place in the commonly accepted ideas of the nature of epidemic cerebrospinal meningitis, that important facts have been kept in the background The very name of the disease and the causative agent have given undue prominence to a single manifestation of a condition that in our opinion is very much more than a cerebrospinal meningitis This is by no means a new idea Others have from time to time expressed the opinion that meningococcus infections are primarily septic in nature and that meningitis is a secondary complication So far as we are aware, however, this conception has not been adopted as a practical working basis for diagnosis or treatment Such prominence has been given the meningitis that the premeningitic stage of meningococcus sepsis has been for practical purposes disregarded It is our view that in a recognition of this primary stage of sepsis lies the key to early diagnosis and a more effective treatment

This point of view has been forced on us by experience of an epidemic of 208 cases in the Base Hospital, Camp Jackson, and has been reached more or less independently by workers at the bedside and workers in the laboratory The practical results have been the recognition of primary meningococcus sepsis in almost half of the cases before the characteristic selective action on the meninges has been exerted, the recognition of abortive cases or of other types of meningococcus sepsis not showing meningitis, the establishment of intravenous serum therapy on a firm basis with notable reduction of mortality and, further, the development of clinical and laboratory methods of diagnosis of proved value

In making this report and in publishing conclusions that are at variance with some existing views we wish to make clear that much of this study was made under what were practically field conditions, in a hospital in the stage of organization, often without heat or even water, with inadequate ward and laboratory equipment and an overworked staff Under these conditions in a certain number of the cases laboratory confirmation of the clinical diagnosis could not be had We fully realize that an absence of finesse possible in civil conditions may

* Submitted for publication March 18, 1918

well be a source of criticism of certain parts of our work and we wish publication made with that understanding

Meningitis is a medical emergency On prompt recognition and vigorous action the life or future wellbeing of the victim depends more than in almost any other acute disease In order to insure early diagnosis, Lieut Col Kent Nelson, Division Surgeon, 81st Division, instructed the regimental surgeons to refer at once to the Base Hospital all men complaining of headache, fever, vomiting or other suggestive symptoms Thus an incomparable opportunity for study of the early stages of these and other acute diseases was offered

Symptoms and Signs—Meningitis is preceded by a stage showing symptoms and signs of a generalized infection This stage lasts from a few hours to three days—averaging about forty-eight hours A few patients with this meningococcus sepsis never develop meningitis These are usually either the abortive or the fulminating cases, rarely those with prolonged course Recognition of the stage of sepsis depends on two kinds of evidence (1) clinical, (2) bacteriologic Approximately one half of our cases were recognized in the premeningitic stage The clinical evidence of the incipient disease is, to the practiced observer, fairly definite, although for certainty laboratory confirmation is usually necessary Description of the early symptoms or signs follows

The fever is rarely above 102 F—more often 99 to 101 The pulse is relatively slow, with frequent vagal irregularities There is a characteristic attitude, manner and facies The patient is not exactly irritable, but is resisting, prefers to be let alone and lies on his side with thighs and knees drawn up, shielding his face with the coverings He is very sensitive to cold and resents exposure The responses are intelligent, but are given in as few words as possible and with the least effort The voice is not modulated, the muscles of expression are not brought into play The voice and expression are "far away" There is a vacant look of apathy and dulness that is almost constant The veins of the temporal region and forehead are full, the eyeballs are tender, and cyanosis of the face is most common This is especially noticeable in the margins of the ears which are purplish in the region of the helix, antihelix and lingula, often with a sharp line of demarcation The pupils are almost always dilated A few cases show slight retinal edema with faint obscuration of the disk margins and fulness of the retinal veins

In a large proportion of the cases there is an upper respiratory tract infection, a coryza, pharyngitis, tonsillitis, laryngitis, rarely bronchitis, in four cases a pneumonia This respiratory involvement is so noticeable that it is more than a coincidence and demands careful

study This was noted in our preliminary report,[1] also by Medlar,[2] Mink,[3] Thomsen and Wulff[4] The oral secretions are often viscid in the extreme, the tongue coated, the breath heavy

The skin manifestations are most important Early there may be a more or less diffuse mottling, giving a lead-colored appearance *Tâche cérébrale* is constant but of slight value in diagnosis A few cases, mostly of the milder type, have shown a macular rash resembling early chickenpox or large rose spots This rash is often very puzzling and characterizes the less severe types The predominant skin sign is the petechial rash This appears about the shoulder or pelvic girdle if at all, next in order of frequency, over the trunk, extremities, face, oral mucosa, and conjunctiva We have not observed it in the retina It appears with astonishing rapidity in crops, and in some of the severe cases the patient may become well dotted within an hour The individual spots are typically petechial, the larger are raised above the skin surface, do not disappear on pressure, vary in size up to 1 cm in diameter and last about three days, leaving a pigmented stain In the presence of an epidemic, such a rapidly developing hemorrhagic rash is diagnostic Purpura is a feature of the fulminating cases This purpura does not arise from the petechial spots, but is a separate lesion It develops with the greatest rapidity, and within a few hours considerable areas of the body surface may be covered

Next to the rash, the reflexes give the most valuable early evidence of the disease In a word, there is an unequal enhancement of the deep reflexes The epigastrics, the knee jerks, the Achilles jerks, all tend to be exaggerated, with inequality In a study of the deep reflexes of the early stages of acute disease in our receiving ward, such increased reflex irritability is found to be common in a variety of infections This increase, however, is uniform on both sides of the body The feature of the altered reflex irritability of meningococcus infection is the lack of uniformity of corresponding reflexes on both sides One case began with a picture resembling that of an acute articular rheumatism, another with that of an acute, purulent meningococcus conjunctivitis Slight chills are common Headache is present in about 85 per cent of the cases It is frontal or vertical, less often lower occipital, may be most severe, and is described as a sense of unbearable pressure or "bursting" It is important to note

1 Herrick, W W Epidemic of Meningitis at Camp Jackson, Jour Am Med Assn, 1918, **70,** 227

2 Medlar, E M Epidemic Cerebrospinal Meningitis at Camp McClellan, Jour Am Med Assn, 1918, **70,** 458

3 Mink, C J Points in the Epidemiology of Meningitis abstr, Jour Am Med Assn, 1916, **66,** 463

4 Thomsen, O, and Wulff, F Meningococcus Infection and Meningitis Hospitalstidende, 1917, **60,** 1192, abstr Jour Am Med Assn, 1918, **70,** 498

that rigid neck, Kernig, and Brudzinski are almost always absent during this stage

The clinical suspicion aroused by any combination of two or more of the signs or symptoms enumerated demands lumbar puncture In the stage of sepsis, the spinal fluid is usually clear, shows in about 60 per cent of the cases a slight increase in pressure, a normal number of cells, reduces Fehling's solution, and may or may not show a trace of globulin Examination after long centrifugation and the evaporation on the slide of several cubic centimeters of the residue remaining after pouring off the supernatant fluid generally reveals one or more pairs of meningococci, almost always extracellular and variable in form and size As noted in our preliminary report,[1] repetition of lumbar puncture within a short time often results in bringing down the organisms which, in our opinion, are first present in the cerebral-intraspinal spaces and find their way into the lower spinal spaces only after lapse of several hours By special methods recently published[5] Capt F W Baeslack, chief of the laboratory, has found meningococci by blood culture in this early stage in 36 per cent of the cases so examined

Clinical types of meningococcus sepsis — Four types may be described — the abortive or atypical, the ordinary, the severe, the fulminating

The abortive types These are mild systemic disturbances without local focus of suppuration Many of these patients have symptoms and signs of meningeal irritation They may present themselves with headache and vomiting, may show a stiff neck, a positive Kernig and increased reflexes, slight fever and evidence of infection of the upper respiratory tract They do not have the rash The spinal fluid may be under increased pressure, but shows no abnormal elements and generally no meningococci The diagnosis depends on the clinical picture and the demonstration of the meningococcus in the spinal fluid, nasopharynx, conjunctivae or blood stream One of these patients who had evidence of meningismus showed an extraordinary high agglutinin titer of the blood The brevity of the duration of these cases is surprising Within twenty-four hours most of them are well, rarely they remain in bed forty-eight hours Their importance is naturally epidemiologic Doubtless in a large epidemic many such cases are undiscovered, being passed over as harmless, upper respiratory tract or other infections They are, therefore, a great menace to susceptible contacts They prove the importance of careful study of every case showing fever and any minor disturbances during the presence of an epidemic The atypical cases are of peculiar interest and will be made the subject of a special report One of these took

5 Baeslack F W, Bunce, A H, Brunelle, G C, Fleming, J S, Klugh, G F, McLean E H Salomon, A V Cultivation of the Meningococcus Intracellularis (Weichselbaum) from the Blood, Jour Am Med Assn, 1918, **70**, 684

the form of a subacute polyarthritis with positive blood culture, a somewhat prolonged course and a prompt response to large doses of serum intravenously Recovery was complete

The ordinary type In these cases the symptoms of the generalized infection usually last thirty-six to seventy-two hours They are as a rule, mild, the rash is usually slight and may be petechial or macular, never diffusely purpuric The evidence of meningitis develops gradually, unconsciousness is rare, and the course may be prolonged The chief emphasis is on the meninges These cases show the typical headache, stiff neck, positive Kernig and Brudzinski signs, altered reflexes, irritability and the purulent spinal fluid Hydrocephalus is a considerable danger and the response to intravenous serum therapy is often less prompt than in the more severe types

The severe type The stage of sepsis usually lasts from eight to forty-eight hours, during which there is evidence of severe toxemia Patients are depressed, uncommunicative and wish to be left alone The upper respiratory tract infection is frequent, with a viscid condition of the oral secretions Fever is rarely above 102 F The feature of these cases is the petechial rash, which appears with the startling rapidity described The patient is profoundly prostrated, and, as a rule, becomes unconscious before any evidence of secondary suppurative foci in the meninges or elsewhere can develop Polyarthritis is common in these serious types Death may occur before any such metastases arise Response to intravenous serum treatment is, as a rule, prompt The most brilliant results with this method are in these grave cases Few therapeutic experiences are so immediately satisfactory The patients often rouse from coma, the rash and other symptoms rapidly recede and within forty-eight hours many are apparently out of danger Intraspinous serum administration alone is usually insufficient to check their downward progress Diagnosis in the premeningitic stage is usually possible The blood culture is generally positive

Fulminating cases These are tragic in the extreme The patient is overwhelmed with a toxemia and may die within a few hours One of our patients lived only four hours after onset of symptoms Another who suffered with a "cold" for three days went to bed at night with slight malaise and was found dead by his fellows early the next morning These patients have a temperature of from 102 to 104 F, a rapid pulse, vomiting, delirium, the petechial rash, and, most characteristic of all, extensive purpura As a rule meningitis is not present Clinical evidence, which may or may not be definite, is readily confirmed by blood culture or by demonstration of meningococci in the spinal fluid In some cases the spinal fluid obtained by lumbar puncture shortly before death has been negative, while that obtained from the lateral ventricles immediately after death has shown meningococci

This emphasizes the importance of our recommendation that lumbar puncture be repeated in doubtful cases to bring down the organisms for diagnostic purposes

The complications—The manifold complications of this epidemic have constituted a strong argument in favor of the view that the disease is primarily a sepsis The purulent character of many of these cases is important After the symptoms of the generalized disease subside such complications may continue to act as a nidus of infection from which relapses may arise or a general toxemia result, retarding or preventing recovery Proper surgical or serum treatment of such a focus is of the greatest importance Nine patients had panophthalmitis The infection reaches the eyes through the ciliary vessels, not the optic nerve sheaths The cornea becomes congested, the iris cloudy Soon the media become opaque, and within a few hours sight is lost The rapidity with which the entire organ is invaded and destroyed is a strong argument for the view that the infection is hematogenous Fortunately, but one of our patients suffered a bilateral panophthalmitis Enucleation has been performed in most of our cases with great improvement in the general condition of the patient The affected eye is a source of pain, of mental and nervous irritability and other evidence of toxemia On microscopic examination these eyes show meningococci in astonishingly large numbers Optic neuritis and retinitis are present in some degree in a large number of cases and are of value in early diagnosis Paralysis of the extrinsic muscles of the eye, most often those supplied by the sixth nerve, has been noted in six cases One of these was bilateral, five were transitory

We have observed but one case of endocarditis This patient developed a relapse with dilated heart, a loud systolic murmur over the precordium, symptoms of sepsis and a positive blood culture At necropsy a few small fresh vegetations were found on the tricuspid valve The myocardium seems to suffer little The pulse rate is slow during the early stages, often rapid during convalescence There were six cases of dry fibrinous pericarditis One of these at necropsy showed the most extensive possible deposit of fibrin in masses, some 5 cm in diameter, over the visceral and parietal layers Two cases exhibited pericardial effusion as a late complication One patient had a temperature ranging to 104 F One hundred and ten c c of bloody purulent fluid were removed, showing meningococci in pure culture, 30 c c of meningococcus antiserum were injected into the pericardial sac with prompt relief of symptoms and disappearance of meningococci in the fluid subsequently aspirated Separate report will be made of these pericardial complications

Pulmonary lesions are not at all uncommon Three patients showed at onset consolidation of part or all of a lower lobe, one a small pleural effusion from which meningococci were grown

Arthritis has been quite a feature of the epidemic One case began as an apparent acute articular rheumatism, in two the arthritis preceded the meningitis, in others this complication appeared late Arthritis in the stage of sepsis, is usually very painful, involves many joints, is not accompanied by much swelling or effusion, but shows local redness, heat and tenderness The picture is almost exactly that of acute rheumatic polyarthritis, but is more transitory The arthritis of the last stage is more generally monarticular, most often involving the knee, is purulent, accompanied by great swelling, but shows little redness and is only moderately painful It is striking that despite the presence of a large purulent exudate in knee joints in the late stage of meningococcus sepsis, there is little muscular spasm or limitation of motion on account of pain Repeatedly the meningococcus has been grown from the pus obtained in these joints Serum has frequently been injected directly into the knee joints with apparent benefit The prognosis of meningococcus arthritis, although a feature of the severe cases, is good and permanent disability is rare

Otitis media has been common, none has required mastoid operation At necropsy, the accessory sinuses of the nose are frequently found filled with pus which in a few instances contained meningococci There have been three cases of monoplegia Nine cases have shown epididymitis or orchitis This has not been suppurative and has subsided in a few days without apparent atrophy The postmeningitis cachexia is notable, although infrequent after intravenous therapy There is emaciation, a waxy pallor of the skin, anemia, irritability, apathy, weakness and vertigo, tachycardia, exaggerated reflexes In this condition it is of the highest importance to make a thorough physical examination Often one of the complications enumerated above is discovered Again, nothing can be found Usually such patients recover after a prolonged period

Two cases have relapsed, one four weeks after convalescence, another, three weeks The second attack may be more severe than the first A special report of these relapsing cases will be made The fact of their occurrence lends discouragement to vaccine prophylaxis and other measures for the production of immunity

A matter of highest importance is the recognition that epidemic cerebrospinal meningitis often occurs during the course of other acute diseases The meningococcus seems to flourish in a soil prepared by any organism or by any condition that will lower the general bodily tone A large number of our cases have developed during the acute stages or shortly after measles, pneumonia, otitis media, tonsillitis, or other infections of the respiratory tract This association deserves special emphasis Meningococcus infections as a complication of other acute diseases gives a confused clinical picture in many instances

The diagnosis here naturally depends almost entirely on the laboratory The clinical acumen must furnish the initial suspicion The change of condition, the fatigue of travel, of unaccustomed drill, homesickness and other new influences to which the recruit is subjected doubtless act in a manner similar to acute diseases in paving the way for meningococcus infections

Necropsy findings—Among the fifty-four deaths in this series of 208 cases, thirty-one necropsies were performed Owing to an overwhelming amount of clinical work and limited equipment, it was impossible to examine all of the dead There was a remarkable dryness of the bodies Section of the muscles resulted in little or none of the oozing usually seen The peritoneum was often lustreless because of this lack of moisture The lungs in many cases were dry and shrunken The liver, spleen and kidneys, while enlarged in many instances, lacked the ordinary amount of fluid This dehydration explains the excessive thirst of so many patients and is the basis of our routine ward order that water be offered every fifteen minutes to those awake

Captain Blakeslee in several cases demonstrated that the exudate was subarachnoid and not immediately subdural He has been unable to find necropsy evidence of suppuration about the cribriform plate of the ethmoid In none of our cases did the macroscopic appearance suggest extension of the process from this point

The following is a summary of the findings Lack of lustre of the meninges without exudate, 1, purulent exudate in the central nervous system, 26, exudate localized in the vertex alone, 7, in the base alone, 3, vertex and base, 16, in the lateral ventricles, 10, parietal region alone, 5, occipital region or cerebellum alone, 0, congestion of meninges without exudate, 5, adhesion of meninges to cortex, 6, blocking of foramen magnum or ventricles, 6 The choroid plexus was in most cases congested and in more than half the number cystic Eleven showed petechiae in the skin, 10, purpura Diffuse purpura was not seen in the serous membranes, viscera or muscles One case having athetoid and convulsive movements of the left side before death showed a large hemorrhage in the right Rolandic area with multiple small hemorrhages throughout the subcortical areas of cerebrum and cerebellum Petechiae are frequent on both visceral and parietal surfaces of the pericardium and peritoneum Four had conjunctival petechiae Heart hypertrophy, 1, dilatation, 1, acute vegetative endocarditis (tricuspid), 1, pericarditis, fibrino-purulent, 4, sero-purulent, 4 Pleurisy was present in 8, lobar pneumonia in 2, bronchopneumonia in 8, lung congestion in 7, abscess in 1 The spleen was enlarged in 22 cases, normal in size 4, in 5 it was not examined Kidney cloudy swelling, 10, congestion, 10 Adrenal congestion, 1

Liver, enlarged and congested, 17, showing cloudy swelling and fatty change in 5. Peritonitis, 1. Suppurative choroiditis, 3.

Treatment.—Based on the conception that the disease is in its early stages a generalized meningococcus sepsis which can be recognized before meningitis or other complications develop, the serum treatment, as established by Jochmann, Flexner and others has undergone modification at our hands. Instead of attacking a metastatic focus of infection in the meninges, we have sought to reach the organism during the stage of systemic invasion by intravenous serum therapy. This measure was at first tried as one of desperation in an attempt to save the life of a member of the staff of the Base Hospital who was stricken with a serious type of the disease. Success led us gradually to develop the present method. Having no standard criteria of such treatment, we have felt our way gradually until, with an experience of over 100 patients treated intravenously, we believe that a safe and satisfactory method has been worked out. Not only does clinical observation seem to justify the method to be described, but statistical study of cases treated by various methods shows that with the newer forms of treatment there is a decrease in mortality. Treatment in this epidemic has passed through three phases, the first phase, of intraspinal therapy alone, the second, of intraspinal combined with timid intravenous therapy, the third, of bold intravenous treatment combined with liberal drainage of the spinal fluid and the use of a considerable, though as a rule, a small amount of serum intrathecally.

On admission a patient presenting a combination of the early symptoms mentioned is subjected to lumbar puncture. If the spinal fluid is cloudy, enough is removed to reduce the intraspinal pressure to an approximate normal and a less amount of serum is at once allowed to run into the spinal canal. If the spinal fluid is clear, no intraspinal injection is made. The fluid is rushed to the laboratory in a thermos container and immediately examined. Meanwhile the patient receives a desensitizing dose to determine sensitiveness. One hour later 50 to 120 c.c. are administered by vein, the first 15 c.c. at the rate of 1 c.c. per minute. Large glass syringes are best for this, as the flow is easily controlled and a cumbersome arrangement of tubes and stopcocks is not necessary. In a case of ordinary severity this intravenous dose is repeated every twelve hours until the temperature becomes normal, or until six or eight injections have been given. In severe cases the serum is repeated every eight hours until the desired results are obtained. In fact, the size and frequency of intravenous serum doses is very like those advised by the group of workers in the Rockefeller Institute in lobar pneumonia of the appropriate type.

We have seen no ill effects from these large amounts of meningococcus antiserum. In a retrospect of the epidemic, our regrets are that

so many cases received doses too small If given at all by vein, the serum must be boldly used Study of Class B cases would seem to show that small amounts may have even a harmful effect It is our belief, however, that this is not the case In a few cases the temperature is seemingly not influenced by the intravenous injections In such the type of serum is changed, an interval of about forty-eight hours is allowed to elapse and another series of doses given So soon as meningitis develops the usual intraspinal injections are given and repeated about once in twenty-four hours for a varying number of days until the organisms disappear from the spinal fluid and lymphocytes make their appearance in numbers With large intravenous injections of serum the meningococci, as a rule, disappear from the fluid within twenty-four to forty-eight hours and repeated intraspinal serum administration is not deemed necessary The greater our experience in intravenous serum therapy in this disease, the more have we attempted sterilization of the blood by massive doses of serum, particularly in the early stages when the positive blood culture and the clinical picture indicate a generalized hematogenous infection When meningitis is established, this treatment is supplemented by repeated spinal drainage, puncture usually being done about half an hour after the intravenous injection Serum is introduced into the spine in amount sufficient to relieve the severe headache which may follow such drainage It is our idea that by thus draining the spinal canal considerable antibody may escape from the blood stream into the upper intraspinal spaces through the choroid plexus Experimental and clinical study of this point is in progress

It is possible to overdo treatment Some of the more prolonged cases, even when meningococci persist in the spinal fluid, do better or even recover promptly when all treatment is stopped This is especially true of the cases that have little fever and in which the serum seems to act as an irritant giving rise to headache, delirium and increased opisthotonus Other treatment is not neglected Second in importance to serum is morphin, which should be freely used, especially in the early stages Chloral and bromid are of minor help in controlling symptoms Nervous patients are given opiates, with or without chloroform, before puncture is made No patient is forcibly restrained during puncture Large amounts of fluid and liberal nourishment are provided

Table 1 shows that the total mortality of the entire series of 208 cases is 26 per cent In the 129 cases treated by intraspinal methods alone or with intravenous serum doses of 10 to 45 c c , it is 31 7 per cent , in 79 treated by larger amounts of serum intravenously and average or smaller amounts intrathecally, 16 4 per cent The mild cases do well by either method of treatment It is in the severe types that the intravenous methods give the most striking results Sixty-two

TABLE 1—EPIDEMIC CEREBROSPINAL MENINGITIS
March 4, 1918 208 Cases

Class	Cases	Deaths	Mortality, per Cent
A1a	36	1	2 7
A1b	17	0	0 0
A2a	15	12	80 0
A2b	24	12	50 0
A	92	25	27 0
B1a	7	0	0 0
B1b	5	0	0 0
B2a	5	2	40 0
B2b	20	14	70 0
B	37	16	43 2
A and B	129	41	31 7
C1a	11	1	9 9
C1b	4	0	0 0
C2a	17	2	11 3
C2b	47	10	21 1
C	79	13	16 4
A, B and C	208	54	26 0

KEY TO TABLE

Class A Cases having intraspinal serotherapy alone

Class B Cases having the usual intraspinal serotherapy and small amounts (10 c c to 45 c c) of serum intravenously

Class C Cases treated with large amounts of serum intravenously with average or small amounts intraspinally

1 Mild cases

2 Severe cases

a Cases with early diagnosis (recognized before the spinal fluid became cloudy)

b Cases with later diagnosis (recognized after the spinal fluid became couldy)

and five-tenths per cent of the serious cases in Classes A and B died, 18 5 per cent of corresponding types in Class C Another important effect of intravenous therapy is the apparent reduction in number of complications, 31 per cent of Class A and B cases showed important complications, 14 per cent of Class C

It may be argued that Class C cases were those from the later stages of the epidemic when the meningococcus might have lost some of its virulence and that the results of intravenous serotherapy are therefore, not better than might have been reached with older methods The possibility is admitted, but is not considered by us a probability Clinically the cases studied in the later phases of the epidemic seemed about as severe as those seen earlier One of the last of our deaths was a fulminating case with purpura

Table 2 shows certain facts of interest It is, however, misleading in that the Class C cases would appear to have received the most active

intraspinal treatment It is to be borne in mind that report is made of the development of a method rather than of the method itself This development extended throughout four months of a large epidemic and a sharp line of separation between various phases of this development is not possible The tables do not, therefore, nor do the descriptions, represent the final method adopted or its results In a future publication it is planned to take this up in detail Table 2 is proof that intraspinal treatment has not been neglected, but it does not correctly indicate the amount of serum given by vein or spine in the fully developed combined method In order to avoid too detailed classification we have arbitrarily placed every case receiving more than 50 c c of serum by vein in Class C Most of our patients are now given from 200 to 600 c c by vein and a lesser average amount intraspinally than the table indicates It is important to note the shorter period of fever and the earlier average disappearance of meningococci from the spinal fluid in Class C It is a common experience to have organisms disappear from the spinal fluid after the first or second massive intravenous serum injection The laboratory workers made special remark of this fact when such treatment began to be used freely

TABLE 2—Summary of Classes A, B and C

Class	Average Number Spinal Punctures	Average Amount Spinal Fluid Out, C c	Average Amount Serum in Spine, C c	Average Amount Serum in Veins, C c	Average Duration of Fever, Days	Average Duration of Meningococci in Spinal Fluid, Days
A and B	4 6	180 2	110 5	38	9	5 5
C	7 2	279 5	138 4	151	7 3	3 1

Ventricular puncture was not done The rapidity with which formation of spinal fluid occurs makes a single puncture of one ventricle rather futile The anatomic situation found at necropsy bears out this impression The effect can be but brief and the operation is one of some magnitude First Lieut S A Cobb, M R C, has devised a method of starting the flow in cases in which it is impossible to secure more than a few drops of thick fluid in patients beginning to show signs of blocking of foramina Chloroform is given, relaxing spasm of the neck muscles Lumbar puncture is then done and the head manipulated with the idea of breaking up adhesions that may be forming about the foramen magnum and floor of the fourth ventricle Necropsy study has shown that it is possible to achieve appreciable mobility of the region The method is often successful in starting the flow and in one instance brought about resumption of respiration when this function had ceased In this case life was apparently saved Liberal drainage in the cases with prolonged course, and the use of Lieu-

KEY TO TABULATION OF MENINGITIS CASES IN TABLE 3

Class A Cases having intraspinal serotherapy alone

Class B Cases having the usual intraspinal serotherapy and small amounts, 10 c c to 45 c c of serum intravenously

Class C Cases treated with large amounts of serum intravenously with average or small amounts intraspinally

1 Mild cases

2 Severe cases

a Cases with early diagnosis (recognized before the spinal fluid became cloudy)

b Cases with late diagnosis (recognized after the spinal fluid became cloudy)

TABLE 3—Data of 208 Cases—

Class	No	Name	Duration of Fever, Days	Developing During or After				Symptoms During Onset and Course of Disease																No Showing Important Comp			
				A Pneumonia	B Mumps	C Measles	D Others	1 Headache	2 Nausea	3 Vomiting	4 Chills	5 Delirium	6 Convulsions	7 Fever, F	8 Pulse	9 Arthritis	10 Coryza	11 Sorethroat	12 Pneumonia	13 Cough	14 Unconsciousness	15 Eruption	16 Backache	A Panophthalmitis	B Arthritis, Mono	B Arthritis, Poly	C Paralysis, elsewhere
A1a	1	Clary	18				Otitis R	+		+				105 3	136		+	+									
	2	Grubb	6					+						99 2	80												
	3	Hickey	9					+		+				100 2	100								+				
	4	Hunter	6					+	+	+				101 0	116							+					
	5	Hooks	13					+	+	+	+			99 6	84	+						+					
	6	Hendrix	9				Otitis R	+						100 0	78		Nystagmus										
	7	Hawkins	8					+			+			102 0	126							+	+				
	8	Wall	0					F+						98 2	100												
	9	Wood	3					F+						102 4	122								+				
	10	Couch	1			+		F+		+				104 0	116								+				
	11	Harris	72*	+	+	+					+			98 0	78											+	
	12	Watkins	9					+		+				98 0	74								+				
	13	Allen	0					+		+				99 2	90												
	14	Epes	2					0+						100 2	80								+				
	15	Green	7	+		+								101 0	100		+	+					+				Deltoid
	16	Smith	2					+						96 0	100												
	17	Cone	2					F+			+			101 0	102			+								+	
	18	Crook	8								+			102 8	83											+	
	19	Marler	4					+		+	+			100 3	102												
	20	McNamara	9				Tonsillitis							97 4	98			+									
	21	Davis	6					F+		+				102 0	106						+						
	22	Moser	0			+								97 0	72							+					
	23	Bethea	4					F+						100 2	98			+				+					
	24	Ponds	6			+		+						99 0	86							+					
	25	Blue	4					F+						105 0	96								+				
	26	Reynolds	2							+				98 0	94			+									
	27	Selff	14		+			0+						97 0	72						+						
	28	Moody	23								+			100 0	92								+				
	29	Delameter	5					+	+	+	+			101 8	72												
	30	Armfield	2					F+			+			102 8	76												
	31	Marlam	9					+						103 0	108												
	32	Williams	3					F+			+			101 2	100				+								
	33	Turner	12				Tonsillitis	+						104 0	110			+									
	34	Guiley	9			+		F+						98 4	64												
	35	Larke	0					+						98 8	72												
	36	Lohse	2											103 1	102												
		Total Average	6	2	2	6	4	28	3	11	10	0	0	101 0	90	1	2	7	1	0	2	6	9	0	0	3	1
A1b	1	Bowden	2			+	+	F+	+					101 4	96							+	+				
	2	Tilley	21*					0+	+	+				99 6	84												
	3	Taylor	13			+		0+	+		+			103 0	92							+					
	4	Thorn	4		+			F+						100 0	90							+					
	5	Graham	5					F+		+	+			101 2	72												
	6	Rose	1		+			+	+					102 0	92							+					
	7	Bass	5					+		+				100 4	90												
	8	Warrenfells	3					+		+	+			100 4	90												
	9	Teezell	4					+		+	+	+	+	97 0	90							+					
	10	Harrelson	3					+		+				103 0	100								+				
	11	Mitchell	9					+			+			100 4	72							+	+				
	12	Burton	27			+		+		+				100 2	90												
	13	Crowell	4			+		+		+				100 4	88												
	14	Lail	0					+						98 0	76						+	+					
	15	Garland	2		+			F+						100 2	92												
	16	Slayton	3					+						98 0	78							+					
	17	Boyd	1			+		+						97 4	74			+				+					
		Total Average	6	0	3	5	1	17	4	8	5	1	1	100 4	90	0	0	1	0	0	1	9	3	0	0	0	0

Reflexes N means normal, + means exaggerated, ++ means hyperactive +++ means very hyperactive, R>L means right greater than left, 0 means absent

* Other cause for fever

—of Cerebrospinal Meningitis

Number Showing Important Complications								Serum Effects: Anaphylaxis			Rashes			Adenitis				Reflexes (On Admittance)											Mis	
C Paralysis, Ocular	D Epididymitis	E Pneumonia	F Pleurisy	G Pericarditis, Dry	G Pericarditis, Fluid	H Otitis Media	I Others	Chill	Collapse	Dyspnea	Erythema	Urticaria	Other Rashes	Cervical	Inguinal	Epitrochlear	General	Neck Rigidity	Kernig	Brudzinski	Patellars	Achilles	Abdominal	Cremasteric	Biceps	Triceps	Babinski	Clonus	Photophobia	Herpes
						+R												+	R>L	0	+	+	+	+	+	+	0	0	0	
												+		+				+++		0	N	N	N	N	N	N	0	0	+	
												+						+	+	+	++	++	+	+						+
																		+	+		+	+					0	0		
																		+	+		+	+	+	+	+	+	0	0	+	
		+				R+L		+										++	++	+	R>L	R>L	+	+			+L			
																		+	+		++						0	0		
										+		+						+	+											
Chicken pox							+											0	0	0										
			+															+	++	0	+	+	0	0	+	+	+	0		+
												+																		
												+						+	+	0	+	+					0	0		
																		+	+	+	+	+	R>L	+	+	+	0	0		
																		+	+		+	+								
																		+	+	+	+	+	0	0	+	+	0	0		
																		+	+	+	+	+	N	N	+	+	0	0		
																		+												
																			+	0	++	+	N	N						
																		+	+	R>L	++	+	N	N	++	++	0	0		
																	+													
																		+	+		+									
																		+	+	+	++	++	+	+	++	++	L	+		
						+R												+	+		+									
Fundi disks indistinct						+												+	+	+	R>J	0								
																			+											
																		+	+	+		+	N	N	++	++				
																		+	+											
		+																+	+											
		+	+											+					++											
																		+	+	R>L	+	+	N	N	+	+	0	0		
																		0	0	0	+	+								
																		0	0											
0	0	3	2	0	0	4	1																							
																		+	+	+	++	++	0	N	0	0	0	0		
					+	+											+													
+						+												+	L>R	+	++	++	R>L	R>L	R>L	R>L	0	0		
																		+	+										+	
																		+++	+++	++	+	0	N	0	R>L	R>L	0	0		
	+			Swelling optic disks														+	L>R	+	R>L	R>L	0		++	++	0	0		
														+				+	+										+	
																		+++	+++											
Unequal pupils																		+	+	+	++	++	N	N	N	N	0	0		+
																		++	+		++									+
																		+	0	+	+	+	N	N	N	N	0	0		
																		+	+											+
																		++	+	R	++	N	N	N	N	N	0	0		+
																		++	++		++		++	++	R>L	R>L	0	0		+
																		+	+	R	+									
1	1	0	0	0	1	2	0																							

TABLE 3 —Data of 208 Cases of—

Class	No	Name	Duration of Fever, Days	Developing During or After				Symptoms During Onset and Course of Disease																No Showing Im portant Comp			
				A Pneumonia	B Mumps	C Measles	D Others	1 Headache	2 Nausea	3 Vomiting	4 Chills	5 Delirium	6 Convulsions	7 Fever, F	8 Pulse	9 Arthritis	10 Coryza	11 Sorethroat	12 Pneumonia	13 Cough	14 Unconsciousness	15 Eruption	16 Backache	A Panophthalmitis	B Arthritis, Mono	B Arthritis, Poly	C Paralysis, elsewhere
A2a	1	Williams	9											100 3	68		Lat nystag						+				
	2	Lynn	14		+			+				+		98 0	96					+	+						
	3	Clinton	D											97 4	74												
	4	Skelton	2D					+						102 0	94		+				+	+					
	5	Ellis	D					+						107 0	156						+	+	+				
	6	Murphy	D			+		+						101 0	120						+	+					
	7	Sells	D			+		+						103 0	70			+					+				
	8	Evans	D			+		F+				+		100 3	80								+	+			
	9	Packs	D					F+				+		103 2	100					+	+	+	+				
	10	Westfield	3					+		+	+			102 0	92						+	+					
	11	Frost	D			+		+						99 2	84		+			+			+				
	12	Hill	D			+								100 0	84					+							
	13	Buchanan	D									+		104 2	104			+			+	+					
	14	Meyers	D					F+		+	+			102 4	104												
	15	Bean	D									+		103 4	100		Purpura				+	+	+				
		Total		0	1	5	0	10	0	2	2	5	0			0	2	2	0	4	8	7	7	1	0	0	0
		Average	9											102 5	95												
A2b	1	Rich	19									+		98 0	100						+	+					
	2	Melden	D									+		100 2	92						+	+					Facial
	3	Cochran	13					+					+	96 8	98											+	+
	4	Sullivan	40*				Tonsillitis	+	+	+	+			99 0	86						+			+			
	5	McMillan	19					F+		+				99 2	112						+	+					
	6	Cook	42*					F+	+	+	+			101 0	100						+	+				+	
	7	Smith	1					+			+	+		98 0	64		+										
	8	Thomas	9					+						98 6	104												
	9	Farrell	5		+					+		+		99 4	84						+						
	10	Port	47D					+						103 2	108					+							
	11	Weathers	4D											100 8	68						+						
	12	Lee	D					+						103 0	104								+				
	13	Greener	D			+		+						101 0	100				+			+					
	14	Gibson	3					0+			+	+		100 0	100												
	15	Moseley	D					F+						98 0	100							+					
	16	Harmage	D											102 5	104												
	17	Page	D			+		+						98 2	106					+							
	18	Josey	4			+		+		+	+			101 2	90			+		+	+	+	+				
	19	Ward	D			+		+						103 6	100				+	+	+						
	20	Denson	D					+		+		+	+	98 8	100						+	+		+			
	21	Sumner	D					+				+	+	99 8	104												
	22	Fringer	23					+						101 6	76											+	
	23	Matthews	?					0+	+					99 0	80							+					
	24	Womack	14					+		+				100 8	88								+	+			
		Total		0	1	4	1	19	3	7	5	7	3			0	1	1	2	4	10	9	3	3	0	3	1
		Average	9											100 0	100												
B1a	1	Grisson	3			+		+						98 0	72					+		+					
	2	Fletcher	2		+			F+		+				103 0	94							+					
	3	Pierce	5			+		+		+				104 0	110					+							
	4	Crews	15					+		+	+			102 0	116							+		+			
	5	Williamson	3											98 0	76								+		+		
	6	Pennington	5					F+		+				98 8	84			+		+							
	7	Smith	2					F+	+					102 0	120												
		Total		0	1	2	0	6	1	4	1	0	0			0	0	1	0	3	0	3	1	1	1	0	0
		Average	4											102 0	100												

—CEREBROSPINAL MENINGITIS—(*Continued*)

C Paralysis, Ocular	D Epididymitis	E Pneumonia	F Pleurisy	G Pericarditis, Dry	G Pericarditis, Fluid	H Otitis Media	I Others	Chill	Collapse	Dyspnea	Erythema	Urticaria	Other Rashes	Cervical	Inguinal	Epitrochlear	General	Neck Rigidity	Kernig	Brudzinski	Patellars	Achilles	Abdominal	Cremasteric	Biceps	Triceps	Babinski	Clonus	Photophobia	Mi…
Number Showing Important Complications								Serum Effects										Reflexes (On Admittance)												Mi…
								Anaphylaxis			Rashes			Adenitis																
Swelling optic disks																		++ ++	++ ++	+	++ ++	+	++ +	++ +	R>L++ N	R>L N	R>L 0	0 0		
	Acute nephritis																													
		+																+++ +	++ R>L	0	0	0	N	N	+	+	0	0		
		+														+	+	+ ++ +	+ ++ +		0 ++	+			R>L	R>L	+		+	
		+																	+	0	N	N			+	+				
																+		+	+ 0	0	++ ++	++ ++	+	+	+ 0	+ 0	0 0	0 0		
0	0	4	0	0	0	0	0																							
+	+					+												0	0	0	N	N	N	N	N	N	0	0		
																		++	++	+	++		0	0						
Choroidal abscess																		+	+	+	++	+	R>L	R>L	+	+	L	0		
						+												+	+	+	R	R	N	N	++	+++	0	0		
																		+	+											
																		+	+	+	+	0					0	0		
																		+	+		++									
						+												++	++											
		+																++	0 ++		0 0	0	0	0	0	0	0	0		
																		+	+		++						0	0		
	+	Swelling optic disks																												
		+																++	+								+	L		
Unequal pupils L>R																					0	++					0	R		
																		++ ++ +	++		++ 0 ++									
1	2	2	0	0	0	3	0																							
																		+ +	+ 0	0	N ++	N	N	+	N	N	0	0		
																													+	
Enucleation left eye																			0	0	+	+								
						+																								
Edema of disks																		+	+ +	+	++									
0	0	0	0	0	0	1	0																							

Class	No	Name	Duration of Fever, Days	Developing During or After				Symptoms During Onset and Course of Disease																No Showing Important Comp			
				A Pneumonia	B Mumps	C Measles	D Others	1 Headache	2 Nausea	3 Vomiting	4 Chills	5 Delirium	6 Convulsions	7 Fever, F	8 Pulse	9 Arthritis	10 Coryza	11 Sorethroat	12 Pneumonia	13 Cough	14 Unconsciousness	15 Eruption	16 Backache	A Panophthalmitis	B Arthritis, Mono	B Arthritis, Poly	C Paralysis, elsewhere
B1b	1	Buzzard	5					F+						101 2	108								+				
	2	Letchworth	9					+	+	+	+			97 0	80												
	3	Brademeyer	7					F+		+	+			102 0	100												
	4	Millwood	3					F+		+				101 0	118							+					
	5	Stillwell	4					+		+				98 6	99							+			+		
		Total		0	0	0	0	5	1	4	2	0	0			0	0	0	0	0	0	2	1	0	1	0	0
		Average	5											101 0	100												
	1	Manley	21											99 6	120												
	2	Grubb	4					+						99 0	80												
	3	Spurlock	8					+	+	+				101 0	100		+	+									
	4	Packer	0					F+						99 0	66		+										
	5	Dukes	D								+			100 4	104			+		+							
		Total		0	0	0	0	3	1	1	1	0	0			0	2	2	0	1	0	0	0	0	0	0	0
		Average	10											100 0	100												
B2b	1	Wetmore	19					+				+		101 2	100							+			+		
	2	Blanchard	12					+						101 0	98					+				+			
	3	Coulter	14					+	+	+				99 2	68						+		+				
	4	Shafner	27					+			+			102 2	82						+			+			
	5	Benner	D					+		+	+			100 2	64												
	6	Murphy	D					+						101 8	110		+					+	+				
	7	Pope	D							+	+			101 8	100							+	+				
	8	Borden	19					+		+				98 2	88						+	+					
	9	Poole	D											101 0	96						+						
	10	Thomas	1		+									103 0	96			+				+					
	11	Dyer	D					+		+				101 4	102			+					+				
	12	Beasley	16					F+		+				97 4	84						+						
	13	Tanner	D									+		103 0	110						+						
	14	Smith	D					+			+			101 0	88		+	+		+			+				
	15	Chandler	D											98 2	88					+	+	+					
	16	Culpepper	D					F+						98 6	84						+	+					
	17	Anderson	D			+								100 0	100												
	18	White	D					F+			+			99 0	82							+	+				
	19	Castles	D											100 0	100						+	+					
	20	Adams	D											103 0	?						+	+					
		Total		0	1	1	0	12	1	6	5	2	0			0	2	3	0	3	10	10	6	2	1	0	0
		Average	10											99 0	90												
C1a	1	Fleming	2					+			+			100 2	104							+					
	2	Latham	5											98 0	80		+			+		+					
	3	Davis	7	+										101 0	98						+						
	4	Hilner	4					0+						100 0	126			+									
	5	Staley	8					+	+	+	+			101 2	80												
	6	Layton	3					+						98 2	76												
	7	Moore	6					T+		+	+			100 8	96												
	8	Thacker	15			+		+						100 4	74							+					Facial, left arm
	9	Galloway	6					+						101 0	110							+	+				
	10	Bray	4					F+		+	+			100 4	112							+					
		Total		1	0	1	0	8	1	3	4	0	0			0	1	1	0	1	1	5	1	0	0	0	1
		Average	6											100 5	100												
C1b	1	Breaux	19					F+			+			99 4	128						+	+	+				
	2	Carkhuff	4					+	+	+				101 0	120												
	3	Arrants	3					+	+	+	+			100 2	88												
	4	Fletcher	14					+		+				103 0	94						+						
		Total		0	0	0	0	4	2	3	2	0	0			0	0	0	0	0	2	1	1	0	0	0	0
		Average	10											101 0	100												

Number Showing Important Complications								Serum Effects: Anaphylaxis			Serum Effects: Rashes			Serum Effects: Adenitis				Reflexes (On Admittance)											Misc	
C Paralysis, Ocular	D Epididymitis	E Pneumonia	F Pleurisy	G Pericarditis, Dry	G Pericarditis, Fluid	H Otitis Media	I Others	Chill	Collapse	Dyspnea	Erythema	Urticaria	Other Rashes	General	Epitrochlear	Inguinal	*Cervical*	Neck Rigidity	Kernig	Brudzinski	Patellars	Achilles	Abdominal	Cremasteric	Biceps	Triceps	Babinski	Clonus	Photophobia	Herpes
								+											+	+	R>L	+	N	N	N	N	0	0		
																		+	R>L	R>L	L>R	L>R								
+																		+	+	+										
																		++	++		++									
																		++	++		0	+								
1	0	0	0	0	0	0	0																							
																		+	+	+	++									+
												+						+++												
																		0	0	0	++									
																		+	+		0									
		+												+																
0	0	1	0	0	0	0	0																							
						+												+++	+		++									
						+																								
								+	+	+		+																		+
						+																								
																		+	+											
																		+	+											
							Hyperemia of disks											+	+	0	0	0	0	0	0	0	0	0		
							Hyperemia of disks											+	+	R	++	R>L	R>L	R>L	N	N	0	0		
							Hyperemia of disks																							
																		+++	+		++									
+		+																												
	+														+															
		+																												
							Erysipelas					+		+																
																		+	+	+	0	0	0	0	0	0	0	0		
1	1	2	0	0	0	3	0																							
	+																	++	++	+	++	+	0	0	0	0	0	0		
																		++	++	+	++	+	+	+	+	+	0	0		
																			+		++	+	+		+	+	0	0		
												+		+				0	0		++									
							Mumps																							
																		++	++	+	++	+	+	+	+	+	0	0		
																					++									
								+		+																				
							Mumps											+	+		++									
	+																													
0	2	0	0	0	0	0	2																							
	+						Mumps											+	+											
														+																
														+		+	+	+	+	+										
														+				+	+		++									
0	1	0	0	0	0	0	1																							

Class	No	Name	Duration of Fever, Days	Developing During or After				Symptoms During Onset and Course of Disease																No Showing Important Comp			
				A Pneumonia	B Mumps	C Measles	D Others	1 Headache	2 Nausea	3 Vomiting	4 Chills	5 Delirium	6 Convulsions	7 Fever, F	8 Pulse	9 Arthritis	10 Coryza	11 Sorethroat	12 Pneumonia	13 Cough	14 Unconsciousness	15 Eruption	16 Backache	A Panophthalmitis	B Arthritis Mono	B Arthritis, Poly	C Paralysis, elsewhere
C2a	1	Merrill	3		+			0+		+				103 0	96						+						
	2	Nelson	2					F+			+			104 0	108						+						
	3	Chastain	13					+	+	+	+			100 0	100							+					
	4	Jamieson	?*					F+		+				100 0	100					+	+	+				+	
	5	McMillan	7					F+						102 0	112			+	+			+					
	6	Smith	?*									+		100 0	104						+						
	7	Letes	7					F+		+				97 4	62												
	8	Stewart	10					F+	+	+	+			99 8	92							+					
	9	Brumley	10					+		+				101 8	86					+		+					
	10	Foster	6					+		+	+			100 0	100						+						
	11	Jenkins	4					+		+	+			104 0	100												
	12	Thomas	D		+			+			+			99 0	74							+					
	13	Workman	D			+	Typhoid Inoc			+				102 0	98			+		+		+					
	14	Heath	5					+						103 0	84		+			+							
	15	Cloer	4					F+						101 0	90		+			+							
	16	Nelson	4					+						99 2	90					+							
	17	Stone .	?					+						102 0	110			+				+					
		Total Average	6	0	2	1	1	15	2	9	6	1	0	101 0	95	0	2	3	1	6	5	8	0	0	0	1	0
C2b	1	Johns	12					F+						100 0	80								+		+		
	2	Moninger	4					+		+	+		+	99 0	78								+	+			
	3	Veasey	22					+	+	+	+	+		98 0	72						+	+					
	4	Walker	*					+	+	+	+	+		101 2	88			Purpura			+	+				+	+
	5	Byrd	15					+				+		99 0	84						+						
	6	Le Fever	6					+	+	+				101 2	116												
	7	Rascoe	7					+		+		+		102 2	102							+					
	8	Cooper	8					+						99 8	96					+		+	+				
	9	Keeble	7					+	+	+				101 0	88												
	10	Wright	3								+			103 8	128		+			+							
	11	Robinson	*					F+	+	+				98 0	126						+	+				+	
	12	Perry	12					+						100 0	102						+						
	13	Stevenson	4					+						98 6	96						+						
	14	Lovelace	14		+		Otitis	1+		+				103 0	102												
	15	Cockerhan	D					F+						100 0	100								+	+			
	16	Runyam	D				Otitis				+			103 0	88												
	17	Romanquera	D											102 4	60						+	+					+
	18	Payne	D			+		F+						98 0	72								+				
	19	Hendrix	0	+			Otitis	+						103 0	96												
	20	Hampton	D								+			104 0	96			+		+							
	21	Frezevant	D					F+				+		100 0	80						+	+					
	22	Berry	D							+				98 0	60			+			+	+					
	23	Drane	21					+						102 2	96										+		
	24	Bell	19					+						101 4	92						+	+	+			+	
	25	Moss	45*					+	+	+				98 0	76			Lat nyst				+	+				
	26	Sanders	21					+			+			102 0	70			+	+				+	+		+	
	27	Little	1					F+	+	+				101 3	96												
	28	Armstrong	2		+			+	+	+		+		102 3	80							+					
	29	Arnold	9					+						102 0	100						+						
	30	Hanley	1									+		98 4	92						+						
	31	Scott	6					+		+		+		102 0	88					+	+						
	32	Davis	2					+						100 6	120			+		+		+					
	33	Shull	4					F+	+					100 0	64						+	+					
	34	Lynch	4		+			+	+	+				101 0	92				+	+							
	35	Lewis	5					F+	+	+				102 3	100		+			+		+					
	36	Holmes	2					+	+	+	+			102 0	90						+						
	37	Ingham	7					F+		+	+			103 2	101						+						
	38	Washington	5					F+			+		+	102 2	80						+						
	39	Wild	2					+	+					104 4	130						+	+					
	40	Black	7					+		+	+			101 2	108												
	41	Jenkins	13					F+		+	+			101 0	100						Peritonsillar abscess						
	42	Hackner	15					+		+				99 0	96							+	+				
	43	Kimball	D					+	+	+				100 0	110						+						
	44	Cross	3					+	+	+	+			103 4	90					+	+						
	45	Ross	17					+	+	+		+		103 4	92		+				+				+		
	46	Catron	17		+			+	+	+		+		105 0	102								+				
	47	Schwartzer	3					+	+	+	+			101 4	102								+				Right ulnar
	48	Chastant	?	+				F+	+	+	+	+	+	101 0	86					+	+	+	+				
		Total Average	10	2	4	1	3	42	19	26	16	11	3	101 5	90	0	3	4	2	9	22	17	12	3	3	4	2

—Cerebrospinal Meningitis—(*Continued*)

Number Showing Important Complications								Serum Effects										Reflexes (On Admittance)											Misc	
								Anaphylaxis			Rashes			Adenitis																
C Paralysis, Ocular	D Epididymitis	E Pneumonia	F Pleurisy	G Pericarditis, Dry	G Pericarditis, Fluid	H Otitis Media	I Others	Chill	Collapse	Dyspnea	Erythema	Urticaria	Other Rashes	Cervical	Inguinal	Epitrochlear	General	Neck Rigidity	Kernig	Brudzinski	Patellars	Achilles	Abdominal	Cremasteric	Biceps	Triceps	Babinski	Clonus	Photophobia	Herpes
																		+	+											
								+	+	+								+	+											
																		++	++	+	++	++	0	0	0	0	0	0		+
Cellulitis Erysipelas							+	+	+	+								++	++		++							+		
														+				+	+		0									
		–	+					+	+	+		+						+	+	+	++									
																		+	+	+	+	++	++	0	0	0	0	0		+
																		++	++											
																		+	+											
	Erysipelas						+											+	+	+										
																		+	+	+										+
																		+	+	++	++									
						+												+	+	+										
																		+	+	+	++	++	+	+	+	+	0	0	+	0
																		+	+	+	++									
																		+	+	+	++									
0	0	1	1	0	0	1	2																							
																		+	+	+										+
																		+	+	+										
		+	+	Gangrene toes				+	+	+			+					+++	++											+
														+				++	++	+	+									
							Mumps							+				++	++	++	+++	++	++	++	++	++	0	0		
																	+	+	++	+										
																		+												
																		+	+		++									
	+	+	+	+														+												
																		+++	++	+++										
					+													++	++	+										
																		++	++											
																		+	+											
Paralysis left arm																		+												
																		+	++											
								+		+								0	0	0										
																		+	++	+	++	+	+	+	+	+	0	0		
							Erysipelas					+						++	++											
	+																	+	++	+	++	+	+	+	+	+	+	0		
Edema of retina																		+	+	+										
						+																								
Recurrence																		++	+		++	++	++	+	+	+	0	0		
+																		+++	++		+									
																		+	+											
+																		+	0		++	+								
												+						++	++	+	++	0	0	0	0	0	0	+		
						+						+						+	+	+	0	0	+	+	0	0	+	0	+	0
												+						++	++	+	++	++	++	++	++	++	0	0		
																		+++	+++	+	0	0								
+											+	+						+	+	+	++	++	+	+	+	+	0	0		
												+						++	+	++	+	0	N	N	N	N	0	0	0	+
												+						+	++	+	0									
												+									++	++								
																		++	++	+										+
																		++	++	+							0	+		+
												+						0	0	0	++									
								+	+	+		+						+	+	+	0	0	0	0	0	0	0	0	0	+
Septicemia								+	+	+		+						++	++	+	0	0	0	0	0	0	0	0	0	+
								+	+	+		+						+	+	+	++	0	0	0	0	0	0	0		
												+						+	+	+	++									+
paresis, recurrence, diabetes insipidus																		+++	++	+	0	0								+
3	2	2	2	2	0	2	2																							

TABLE 4—Epidemic Cerebrospinal Meningitis. Summary of 208 Cases in Classes

Class	Cases	Development During or After: A Pneumonia	B Mumps	C Measles	D Others	Symptoms During Onset and Course of Disease: 1 Headache	2 Nausea	3 Vomiting	4 Chills	5 Delirium	6 Convulsions	7 Fever	8 Pulse	9 Arthritis	10 Coryza	11 Sorethroat	12 Pneumonia	13 Cough	14 Unconsciousness	15 Eruption	16 Backache	Number Showing Important Complications: A Panophthalmitis	B Arthritis, Mono	B Arthritis, Poly	C Paralysis, elsewhere	C Paralysis, Ocular	D Epididymitis	E Pneumonia	F Pleurisy	G Pericarditis, Dry	G Pericarditis, Fluid	H Otitis Media	I Others
A1a	36	2	2	6	4	28	3	11	10	0	0	101.0	90	1	2	7	1	0	2	6	9	0	0	3	1	0	0	3	2	0	0	4	1
A1b	17	0	3	5	1	17	4	8	5	1	1	100.4	90	0	0	1	0	0	1	9	3	0	0	0	0	1	1	0	0	0	1	2	0
A2a	15	0	1	5	0	10	0	2	2	5	0	102.5	95	0	2	2	0	4	8	7	7	1	0	0	0	0	0	4	0	0	0	0	0
A2b	24	0	1	4	1	19	3	7	5	7	3	100.0	100	0	1	1	2	4	10	9	3	3	0	3	1	1	2	2	0	0	0	3	0
B1a	7	0	1	2	0	6	1	4	1	0	0	102.0	100	0	0	1	0	3	0	3	1	1	1	0	0	0	0	0	0	0	0	1	0
B1b	5	0	0	0	0	5	1	4	2	0	0	101.0	100	0	0	0	0	0	0	2	1	0	1	0	0	1	0	0	0	0	0	0	0
B2a	5	0	0	0	0	3	1	1	1	0	0	100.0	100	0	2	2	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
B2b	20	0	1	1	0	12	1	6	5	2	0	99.0	90	0	2	3	0	3	9	9	6	2	1	0	0	1	1	2	0	0	0	3	0
C1a	10	1	0	1	0	8	1	3	4	0	0	100.5	100	0	1	1	0	1	1	5	1	0	0	0	1	0	2	0	0	0	0	0	2
C1b	4	0	0	0	0	4	2	3	2	0	0	101.0	100	0	0	0	0	0	2	1	1	0	0	0	0	0	1	0	0	0	0	0	1
C2a	17	0	2	1	1	15	2	9	6	1	0	101.0	95	0	2	3	1	6	5	8	0	0	0	1	0	0	0	1	1	0	0	1	2
C2b	48	2	4	1	3	42	19	26	16	11	3	101.5	90	0	3	4	2	9	22	17	12	3	3	4	2	3	2	2	2	2	0	2	2
Total Average	208	5	15	26	10	169	38	84	59	27	7	101.0	96	1	15	25	6	31	60	76	44	10	6	11	5	7	9	15	5	2	1	16	8

tenant Cobb's method when drainage is slight and symptoms persist with occasional intravenous injections of serum have given us the most satisfactory results in these difficult cases

It has not been found necessary to follow the blood pressure either during withdrawal of spinal fluid or while giving serum intraspinally In many hundred lumbar punctures and serum treatments no serious symptoms were observed The well known serum effects were noted but do not require description Only one case showed serious anaphylaxis

Visitors to the wards where the patients are treated by the methods described remark on the absence of delirium and of the lack of subacute and chronic cases with cachexia, delirium, hydrocephalic cries and the distressing picture of the prolonged cases In a large number the nutrition suffers little Some patients with stormy onset ask to be allowed up and about on the fourth day There is an air of cheerfulness and optimism about the patients, reminding one of a convalescent surgical ward The proof of the value of this therapy is found in the shortened course, the diminished number of complications the greater comfort of the patients, the prompt disappearance of meningococci from the spinal fluid and the decreased mortality

CONCLUSIONS

1 A camp epidemic of 208 cases of cerebrospinal meningitis is reported

2 The disease is in most, probably in all, instances a primary meningococcus sepsis with usual, but not necessarily universal, secondary meningitis

3 The diagnosis can be made in at least 50 per cent of the cases in the premeningitic stage of sepsis

4 Treatment by large amounts of antimeningococcus serum intravenously, combined with active spinal drainage and intraspinal serum administration, has reduced the duration of the disease, the number and severity of complications and the mortality

Acknowledgment is heartily given Capt F W Baeslack, M R C, who with his staff has done invaluable work in the laboratory without which the clinical work of this epidemic could not have been carried out Captain Baeslack's important contribution will be reported separately[5]

Capt George A Blakeslee, M R C, has made neurologic observations, the necropsies, and has had general supervision of therapy To his careful attention to details and valuable suggestion much of the therapeutic success is due A separate report of the neurologic aspect of the epidemic will be made by him

To the officers who from time to time have served on the Meningitis Squad acknowledgment of skilled and devoted service is made, Capts D L Walker, H S Fincke and E W Barron, First Lieuts B Lattin, G M Parkhurst, Q H Barney, A M Dannenburg, L H Taft, F W Rogers, R C Davis, S A Cobb

I am indebted to S A Cobb and R C Davis, First Lieutenants, M R C, for the accompanying tabulation of the epidemic

BOOK REVIEW

Book Review A Textbook of the Practice of Medicine, by James M Anders, M D, Ph D, LL D, Professor of Medicine and Clinical Medicine, Medico-Chirurgical College Graduate School, University of Pennsylvania, Thirteenth Edition Thoroughly Revised with the Assistance of John H Musser, Jr, M D, Associate in Medicine, University of Pennsylvania Octavo of 1259 pages, fully illustrated Philadelphia and London W B Saunders Company, 1917 Cloth, $6 00 net, Half Morocco, $7 50 net

This is essentially a textbook of internal medicine and diagnosis and as such will be welcomed by both medical students and practitioners

The present, thirteenth, edition has been thoroughly revised, and several subjects entirely rewritten, and the presence of a thirteenth edition is sufficient to prove that it has met the requirements of the profession In general the work is carefully compiled and up to date, convenient for reference and presents the material in an accessible form, being concise, and at the same time sufficiently elaborate for students

The authors have been successful in their effort to correlate pathology and morbid physiology with the clinical and therapeutic aspects of disease and throughout the book emphasized the necessity of recognizing the interdependence of the two phases In addition to a section on "Diseases of the Nervous System," there has been added a wealth of modern material on focal infection, kidney function tests, asthma, acidosis in diabetes, anaphylaxis of food and many other subjects

Particularly useful are the diagnostic tables with the stated aim of giving a practical working knowledge of contrasting features that present points of similarity at the bedside The authors further emphasize the difference between causal and symptomatic treatment of disease, recognizing the importance of each, yet maintaining a distinction between the two

The subject matter is arranged in systems, as Infectious Diseases, Diseases of Metabolism, Diseases of the Respiratory System, etc, and each topic is discussed under the headings of Definition, Pathology, Etiology, Clinical History, Complications, Diagnosis and Differential Diagnosis, and Treatment, with numerous historical notes

The plates, charts and illustrations are good but rather meager, and while a work of this sort cannot be profusely illustrated, there are many points at which an added illustration would be of great assistance to the student Nothing has been overlooked to make the book thorough and accessible, even to anticipating the student's habit of underlining by very successfully italicizing the key words throughout

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EXPERIMENTS ON THE VASOCONSTRICTOR ACTION OF BLOOD SERUM *

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PART 1

INTRODUCTION

The power of blood after clotting or defibrination to constrict blood vessels, as evidenced by its action on perfused organs or on the excised arterial strip, has been frequently observed and to some extent studied as to its nature and origin The work here presented has shaped itself into a study of the vasoconstrictor substance in relation, first, to unclotted blood second, to the cellular and noncellular elements of the blood, third, to certain biologic, physical and chemical reactions, and lastly, to the process of coagulation The literature will be reviewed in much the same order External events have brought the work to a close while it was in many respects incomplete, nevertheless we feel justified in recording it as it stands It was suggested by the work of two of us[1] in 1912 and certain of the conclusions as to the origin of the vasoconstrictor substance from blood platelets and its ability to resist heat or pass through a celloidin membrane were arrived at independently, although a more thorough search of the literature revealed previous work on the same points

LITERATURE

The stimulating action of blood serum, or defibrinated blood, on the arterial wall has long been known As early as 1869 Ludwig and Schmidt[2] on perfusing the muscle of the dog, encountered an unex-

* Submitted for publication March 1, 1918

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* The experiments described in this article were terminated before completion because Drs Janeway and Park entered on war duties The paper was written by Dr Richardson All of the writing except Part III was supervised by Dr Janeway before his death

1 Janeway, T C, and Park, E A Jour Exper Med, 1912, **16,** 541

2 Ludwig, C, and Schmidt, A Arb a d physiol Anstalt z Leipzig, 1868, p 1

pected resistance to the flow of defibrinated blood Five years later Mosso,[3] on beginning to perfuse the kidney of the dog, found that the defibrinated blood used failed for several minutes to flow These observations were confirmed by a number of observers, including Bernstein,[4] Pfaff and Tyrode,[5] Battelli,[6] and others to be mentioned They used a variety of preparations, including all manner of perfused organs, as well as the excised strip of ox artery developed by Meyer[7] Two main explanations for the phenomenon were given Stevens and Lee[8] and Brodie[9] attributed it to some substance formed during coagulation, whereas Meyer,[7] Schlayer,[10] and Broking and Trendelenburg[11] attributed it to epinephrin

This question was settled mainly by O'Connor,[12] who first tested the serum by means of a pair of biologic preparations, the first of which reacted to epinephrin by constriction, the second by relaxation Such a pair was the frog perfusion preparation and the excised segment of rabbit intestine Serum proved to constrict both, and further, resisted procedures calculated to destroy epinephrin Moreover, by comparing plasma with the corresponding serum, O'Connor was able to demonstrate that the "substances which simulate epinephrin get into the blood during the process of clotting"* Investigation of plasma from the peripheral circulation by the same method failed to give evidence of epinephrin Very shortly afterwards Stewart[13] recommended a similar pair of test objects and by the use of them was led to the conclusion that "no evidence is obtained of the presence of adrenalin [epinephrin] in detectable amounts in normal blood taken from the general circulation"

The work of O'Connor is also in accord with the observations mentioned of Stevens and Lee[8] and of Brodie[9] as to the relation between coagulation and the production of vasoconstrictor power It was con-

3 Mosso, A Arb a d physiol Anstalt z Leipzig, 1874, **9,** 156

4 Bernstein, J Pfluger's Arch f path Anat, 1877, **15,** 575

5 Pfaff, F, and Vejnx-Tyrode, M Arch f exper Path u Pharmakol, 1903, **49,** 324

6 Batelli, F Jour de physiol et de path gén, 1905, **7,** 625, *Idem* p 651

7 Meyer, O B Ztschr f Biol, 1906, **48,** 352

8 Stevens, L T, and Lee, F S Studies Biol Lab, Johns Hopkins Univ, 1884, **3,** 99

9 Brodie, T G Jour Physiol, 1903, **29,** 266

10 Schlayer Deutsch med, Wchnschr, 1907, **33,** 1897

11 Broeking, E, and Trendelenberg, P Deutsch Arch f klin Med, 1911, **103,** 168

12 O'Connor, J M Munchen med Wchnschr, 1911, **58,** 1439 Ibid, Arch f exper Path u Pharmakol, 1912, **67,** 195

13 Stewart, G N Jour Exper Med, 1911, **14,** 377

* This and following quotations from foreign journals are translations made by H B R

firmed, at least in part, by Trendelenburg[14] Schultz,[15] in studying another problem, obtained the same result, which has since been confirmed by a number of observers Stewart,[16] using a properly chosen pair of biologic test objects, failed to find evidence of epinephrin in human serums Stewart and Harvey[17] confirmed O'Connor's results in regard to the formation of the vasoconstrictor substance during coagulation, and, moreover, demonstrated its power to constrict the coronary as well as the peripheral arteries Janeway and Park,[1] using parallel preparations of carotid and coronary, were able to "confirm completely the conclusion of O'Connor, Stewart, and Schultz, that the vasoconstrictor substance found in blood serum was not epinephrin" They observed no effect due to uncoagulated blood of ox or rabbit Further, "the examination of uncoagulated blood from six persons with high blood pressure failed to show the presence of epinephrin or other constricting substances"

The vasoconstrictor substance of serum is therefore not epinephrin Further proof to this effect is furnished by the experiments in which apocodein prevented the vasoconstrictor action of epinephrin, but not that of serum For example, Battelli[6] states that apocodein retards, but does not prevent, the action of the "vasoconstrictines" of serum Stewart and Harvey[17] noted that a dog's kidney, after perfusion with apocodein in sufficient concentration to destroy its sensitiveness to epinephrin, still reacted by diminution of flow to boiled serum The like was found by Kaufman[18] to be true of the perfused ear of rabbit

The explanation of the origin of the vasoconstrictor power of serum was more closely approached by Stewart and Zucker[19] in their exhaustive study on serum as compared to plasma and other body fluids on various biologic preparations Of these the frog perfusion preparation and the excised arterial strip gave little or no reaction to citrated plasma and a marked constrictor action to serum to which citrate had been subsequently added Between herudin plasma and serum to which herudin had been added there was a difference "not so strongly marked as in the case of the citrate material" They concluded that the vasoconstrictor property is developed during the process of coagulation, and "not mainly" in connection with the actual change of fibrinogen to fibrin, and is associated with changes undergone probably by formed elements of the blood when it is shed

This last conclusion leads to the relation between the vasocon-

14 Trendelenberg, P Munchen med Wchnschr, 1911, **58,** 1919
15 Schultz, W H Bull 80, Hyg Lab, U S P H and M-H S, 1912, p 37
16 Stewart, G N Jour Exper Med, 1912, **15,** 547
17 Stewart, H A, and Harvey, S C Jour Exper Med, 1912, **16,** 103
18 Kaufman, P Zentralbl f Physiol, 1913, **27,** 527
19 Stewart, G N, and Zucker, T F Jour Exper Med, 1913, **17,** 152, *Ibid*, 1913, **17,** 174

strictor action of serum and the formed elements of the blood On page 172 of the article cited Stewart appends a footnote, "Since this was written we have found that extracts of platelets obtained from citrate blood, the plasma of which is totally inactive, exert a strong constricting effect on artery rings" O'Connor[12] had also mentioned in passing that "extracts of blood platelets of rabbit, obtained from citrated plasma by centrifuging, decanting and dissolving the sediment, rich in platelets, have a powerful effect on the frog vessels" Zucker and Stewart[20] confirmed their previous observation, as did Le Sourd and Pagniez[21] for platelets of a species different from that which furnished the excised artery used for the test

The few observations on record as to the vasoconstrictor effect of erythrocytes are less in agreement All these were made on the frog perfusion preparation Heubner,[22] in studying viscosity, noted in a single experiment that defibrinated blood, if laked and restored to tonicity, causes less constriction of the frog vessels than if diluted with a corresponding amount of Locke's solution Broking and Trendelenburg observed that diluted serum caused more vasoconstriction than laked erythrocytes diluted to produce the same viscosity Hirschfeld and Modrakowski[23] observed, with erythrocytes laked either by means of distilled water or by a specific hemolytic reaction, a marked vasoconstrictor effect In two experiments, however, the erythrocytes laked by the former method caused dilatation These observers failed to record the exact speed of centrifuging or to give evidence of any attempt to rid the cells examined of blood platelets, which are in themselves extremely active Kaufman,[18] who states that "when we laked thoroughly-washed erythrocytes in distilled water or ether, we obtained a strongly vasoconstrictor fluid," is open to a similar criticism

Studies of relation of the leukocytes to the vasoconstrictor substance have been limited to the effect of extracts of certain organs Of these, spleen, bone marrow, and thymus may conceivably be regarded as analogous to blood cells According to Zucker and Stewart[20] these organs, extracted by a method which yielded from the platelets powerful vasoconstrictor substance, are inactive Kaufman,[24] though agreeing as to the thymus, obtained an active substance from the spleen

The effect of plasma as compared to serum has been discussed The effect of plasma as compared to Locke's solution needs further comment It is to be noted that many observers diluted the plasma before testing it, or else used a considerable percentage of citrate In

20 Zucker, T F, and Stewart, G N Zentralbl f Physiol, 1913, **27,** 85
21 Le Sourd, L, and Pagniez, Ph Compt. rend Soc de biol, 1914, **76,** 587
22 Heubner, W Arch f exper Path u Pharmakol, 1905, **53,** 218
23 Hirschfeld, L, and Modrakowski, G Munchen med Wchnschr, 1911, **58,** 1494
24 Kaufman, P Zentralbl f Physiol, 1913 **27,** 530

our present experience this substance is deleterious in concentration of 0.5 per cent within a few minutes. In a previous publication of two of us,[1] as well as that of Sakai and Hiramatsu,[25] the same effect was noted. O'Connor,[12] who stated that plasma had no effect, Stewart and Zucker,[10] that it had little or no effect, and Sakai and Hiramatsu,[25] that it had a vanishingly small effect, diluted the plasma before testing it. Stewart and Zucker used a concentration of citrate as great as 1 per cent. Kaufman,[18] on the other hand, who observed a vasoconstriction, used undiluted citrated plasma. Further, when neither of the objections mentioned apply, as with hirudin plasma, more or less vasoconstrictor effect was noted (Trendelenburg,[14] Kahn,[26] Stewart and Harvey[17]). Proof is therefore lacking that shed plasma has no tonic effect on the arterial wall; still more obscure is the question whether the circulating plasma has a tonic effect on the intact vessels.

The action of serum on smooth muscle, as opposed to the action of epinephrin, has already been discussed. Attempts to define its chemical nature have yielded contradictory results, even on so elementary a point as its classification as protein or crystalloid. The former alternative is supported by Battelli,[6] who observed that the vasoconstrictor substance of serum was destroyed at a temperature of from 56 to 58 C.; by Handovsky and Pick,[27] who observed that it failed to pass through parchment, and that it was not found in the fraction incoagulable by boiling. Kaufman[18] found it insoluble in alcohol or ether. Yanagawa[28] attributes to albumin the action of serum in decreasing the perfusion rate of the excised mammalian heart. Interpretation of his results from the present point of view is complicated by the fact that the hearts used continued to beat. Sakai and Hiramatsu[29] confirmed the failure of the active substance to dialyze through parchment, to resist boiling or to be taken up in alcohol, but unlike Yanagawa, state that it is precipitated with the globulin fraction.

The nonprotein nature of the substance is supported by the work of Schlayer,[10] who observed that it was destroyed neither by a temperature of 56 C., nor by removal of the proteins. His observation that it is not diminished by fifty-eight hours of dialysis is coupled with the statement that epinephrin dialyzes very poorly. This is so at variance with the work of Comesatti[31] that it is permissible to doubt the per-

25. Sakai, S., and Hiramatsu, T.: Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo, 1914, **13,** 177.

26. Kahn, R. H.: Pfluger's Arch., 1912, **144,** 251.

27. Handovsky, H., and Pick, E. P.: Arch. f. exper. Path. u. Pharmakol., 1912, **71,** 62.

28. Yanagawa, H.: Jour. Pharmacol. and Exper. Therap., 1916, **8,** 89.

29. Sakai, S., and Hiramatsu, T.: Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo, 1916, **15,** 397.

30. Voegtlin, C., and Macht, D. I.: Jour. Am. Med. Assn., 1913, **61,** 2136.

31. Comesatti, G.: Arch. f. exper. Path. u. Pharmakol., 1909, **60,** 233.

meability of the membrane used Stewart and Harvey[17] state that the vasoconstrictor substance resists boiling and is soluble in alcohol, Stewart and Zucker[19] that it resists boiling and is insoluble in alcohol, Zucker and Stewart[20] that it can be extracted with alcohol, also by acetone and ether The last-named observer says, moreover, that platelet extract also can be extracted with alcohol Kaufman[08] found that the active substance, though insoluble in alcohol, resists boiling and dialyzes readily through an artificial membrane, and that the dialyzate gave negative tests for protein Voegtlin and Macht,[30] by extracting dehydrated blood, serum, plasma, or erythrocytes with chloroform and extracting the dried filtrate with methyl alcohol, obtained a "white crystalline residue" related to cholesterol This substance resisted boiling in alkaline mediums, and had a tonic action on the vessels of the perfused frog preparation and of the rabbit's ear, as well as on the heart of cold-blooded animals A substance of the same characteristics was isolated from the adrenal cortex

If all the above observations hold good, one must conclude that the vasoconstrictor substance is and is not dialyzable, does and does not resist heat, if a protein is or is not a globulin, and if a crystalloid possesses extreme versatility in its ability to be extracted by various solvents Perhaps a part of the confusion may be explained by absorption of the active substance by the colloids of the blood In the study of the effects of platelet extract the bulk of these are removed by the simple process of decantation

That the vasoconstrictor substance is elaborated during the process of coagulation is clear, that the relation is more than a coincidence, is not Specimens of herudinized blood or plasma which are actively vasoconstrictor do not necessarily contain a clot (Kahn[26]), nor does clotting necessarily occur later (Kahn,[26] Stewart and Zucker[19]) The latter[32] found no difference between clotted and unclotted cystic fluid in its effect on the arterial ring, and had previously concluded, as mentioned, that the vasoconstrictor property is developed "not mainly in connection with the actual change of fibrinogen to fibrin"

The foregoing review of the literature reveals a general agreement to the effect that blood serum is vasoconstrictive, and that this action is not due to epinephrin The rather fragmentary observations on the effect of platelet extract are also in accord, to the effect that the extract has a powerful vasoconstrictor action The work on erythrocytes is inconclusive, on the leukocytes, of questionable relevancy The question of the vasoconstrictor effect of circulating plasma is not settled, and the relation of the vasoconstrictor substance to the factors concerned in coagulation has hardly been touched on The following is an attempt to throw light on these questions

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32 Stewart, G N, and Zucker, T F Jour Exper Med, 1913, **17,** 174

Technic—The test object used throughout was the excised strip of ox carotid, as described by O B Meyer[7] Arteries of the dog and the pig were tried, but found to be too insensitive The apparatus consisted of a large tank suitable for warming the material to be tested, and was kept at body temperature by means of an electric thermostat which gave a very constant temperature within half a degree centigrade The apparatus was grounded to prevent the accumulation of electrical charges A small glass tube suitably bent served both as an attachment for the lower end of the artery and as a tube for the ingress of oxygen, a constant flow of which was insured by the use of a large tank The upper end of the arterial strip was attached to a very light aluminum lever which magnified 15½ The apparatus was so arranged that the artery could be attached at ease to tube and lever, and all three lowered into the arterial chamber This was made from an ordinary Wassermann tube, and had a capacity of 8 c c, although 3 or 4 c c sufficed to cover the artery The chamber was suspended in the warm bath It could be emptied by suction through a suitably bent glass tube fused to the bottom This arrangement permitted a rapid and complete exchange of fluids with little mechanical disturbance Such short exposure to air, and even exposure as long as five minutes, did no demonstrable damage to the artery The apparatus was so arranged that two arterial strips could write simultaneously on the same drum

The arteries were obtained from a slaughterhouse about one hour's journey from the laboratory They were taken from the animal within a few minutes of death, and were put in a bottle containing about 800 c c of cold Ringer-Locke solution They were transported and kept on ice They continued viable for from one to four days, according to the season Transfer into fresh cold Ringer-Locke seemed to improve their viability

A segment of artery about 8 mm long was cut, usually from about the central portion of the artery as obtained The contracted peripheral end seemed equally sensitive, except in hot weather The segment was slit longitudinally, so that the tension was exerted on the circular fibers A needle was passed through the corners at one end of a strip, and a silk ligature tied central to the needle The ligature was then threaded and drawn through The same process was repeated at the other end This procedure prevented slipping of the ligature The strip, except as otherwise indicated, was stretched by 90 gm tension for twenty minutes and then weighted with 30 gm for the tests

The physiologic fluid used will be referred to as Ringer-Locke solution It contained

Sodium chlorid (NaCl), 0 9 per cent , potassium chlorid (KCl), 0 042 per cent , sodium bicarbonate ($NaHCO_3$), 0 03 per cent , calcium chlorid ($CaCl_2$), 0 024 per cent (Dextrose 0 1 per cent)

The dextrose was omitted after Experiment 43, until Experiment 123, when it was again used as its absence was found to facilitate spontaneous rhythmic contractions

The technic described was adequate to detect epinephrin in Ringer-Locke solution in a concentration of 1 to 25,000,000, sometimes of 1 to 50,000,000 or 100,000,000 in cool weather The sensitiveness is, however, subject to influences not well understood, such as heat, or too many minute's delay in removing the artery from the dead animal As already mentioned, sodium citrate damages the preparation The same is true of sodium oxalate, although herudin proved to be innocuous Therefore, all experiments in which the arterial strip failed to prove its sensitiveness in the presence of the anticoagulant employed were discarded For this control, usually serum, sometimes platelet extract or epinephrin, was employed Experiments in which clotting could be demonstrated were also discarded

PART II

SOURCE OF THE VASOCONSTRICTOR SUBSTANCE

Defibrinated Blood —Although the effect of defibrinated blood on the excised artery has been noted by many observers, it may be well to illustrate it (Figs 3, 4, and 13) Its chief characteristics are the immediate onset, the abruptness and the extent of the constriction

Uncoagulated Blood —Blood of the Ox —Blood of the ox was first investigated because it was from the ox that the test-object was obtained

Method —Blood of the ox was obtained as follows A wide-mouth bottle of one liter capacity, and cork, were paraffined A 3 8 per cent sodium citrate solution was prepared This concentration is isotonic (Rous and Turner[33]) As the solution proved to be acid to litmus it was neutralized with dilute sodium hydroxid (NaOH) to a pH of 6 8 to 7 6 (Levy and Marriott[34]) The animals were usually slaughtered by cutting the neck The bottle, containing a suitable amount of citrate, was held under the stream of blood and filled instantaneously It was then inverted several times and brought to the laboratory in a pail of cracked ice Here the volume was measured and the maximum concentration of citrate calculated This varied from 0 6 to 0 3 per cent The increase of volume resulting from the addition of citrate was less than one fifth The mixture was strained through two layers of fine gauze to ascertain the presence of clots The fluids were tested in the following order

1 Ringer-Locke solution

2 Ringer-Locke solution minus calcium

3 Ringer-Locke solution containing citrate in the same concentration as the blood to be investigated

4 Uncoagulated (citrated) blood, this was allowed to remain in contact with the artery as long as seemed feasible without damaging it, usually three or four minutes

5 Defibrinated blood to which citrate in the above concentration had been added after defibrination, the object being to prove that the preparation had retained its sensitiveness in the presence of citrate

In the case of the herudinized blood the order was as follows

1 Ringer-Locke solution

2 Ringer-Locke solution containing herudin in the same concentration as the blood to be tested

3 Herudinized blood

4 Defibrinated blood to which herudin in the same concentration had been added after defibrination

In some of the later experiments herudin was omitted from the defibrinated blood because of its scarcity, its innocuousness with respect to the excised artery having been amply demonstrated

Results —Eighteen specimens of citrated ox blood were examined Of these, eight experiments were discarded because the sensitiveness of the artery was insufficient or unproved, and one because the concen-

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33 Rous, P, and Turner, J R Jour Exper Med, 1916, **23,** 219

34 Levy, R L, and Marriott, W McK The Archives Int Med, 1915, **16,** 389

TABLE 1—CITRATED OX BLOOD

Experiment	Constriction	Citrate, Per Cent	Material Obtained
61	0	0 5	1 day previous
66	+	0 5	1 day previous
99	+++	0 5	Same day
146	0	0 5	Same day
	0	0 5	Same day
149	0	0 48	Same day
	—	0 62	Same day
152	0	0 3	Same day
	—	0 33	Same day

Explanation of Tables

Under "Constriction" is recorded the reaction of the artery
++++ = maximal constriction
++ = marked constriction
+ = moderate constriction
Trace = slight constriction
0 = no constriction
— = dilatation
Under "Material Obtained" is recorded the time elapsed between collecting and testing the material

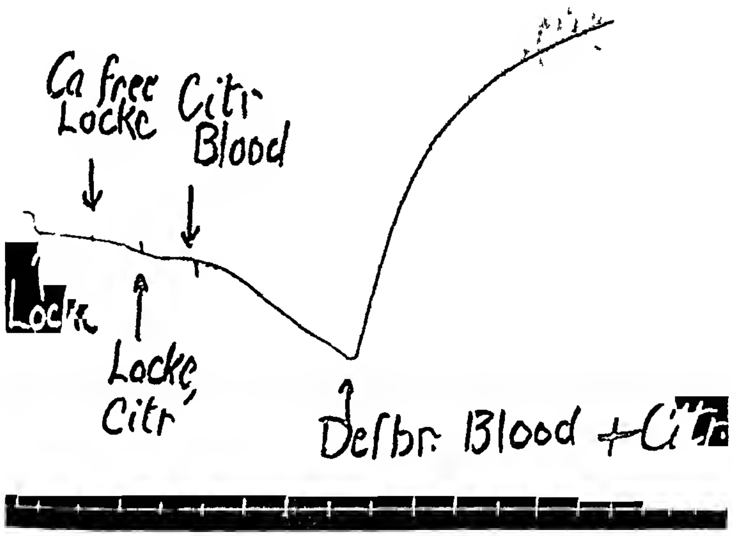

Fig 1—Experiment 149 Ox carotid Citrated ox blood Order of tests (1) Ringer-Locke solution, (2) same without calcium, (3) Ringer-Locke solution containing 0 62 per cent sodium citrate, (4) ox blood containing 0 62 per cent sodium citrate, (5) defibrinated blood containing same Time in minutes in all figures except as otherwise indicated

tration of citrate used (0 25 per cent) seemed too small Of the remaining nine specimens, as shown in Table 1, seven caused no change or else a moderate fall of tonus, whereas only two caused a rise A typical example of the lack of vasoconstrictor action is shown in Figure 1, in which substitution of citrated blood for citrated Ringer-Locke solution caused a moderate relaxation lasting three and one-third minutes, at the end of which the arterial strip reacted vigorously to defibrinated blood to which sodium citrate in the same concentration had

been added Similarly, in Figure 2, citrated blood caused only a very slight delayed rise followed by a slight fall At the end of eight and one-half minutes the arterial strip showed extreme sensitiveness by the degree of its response to citrated plasma In the two cases in which a vasoconstrictor action was observed, no careful examination for clot was made, as was done in the subsequent experiments Our suspicion that the rise was due to partial clotting was therefore not confirmed The large proportion of specimens that had no vasoconstrictor effect, however, justifies the conclusion that citrated blood of the ox, as obtained, has no constrictor effect on the excised ox artery

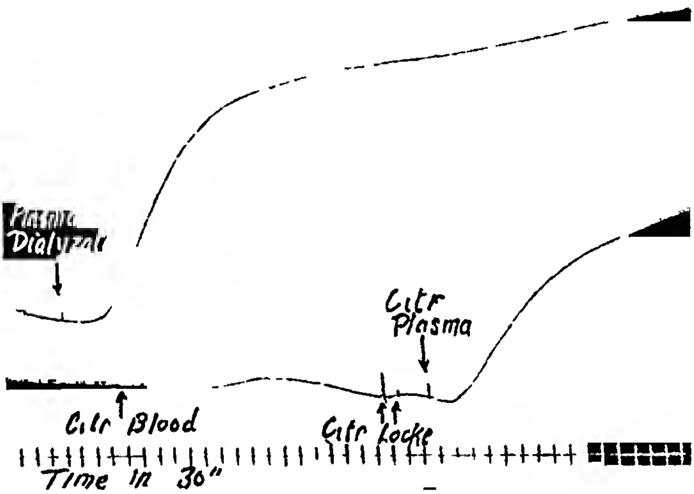

Fig 2—Experiment 61 Ox carotid Ox blood Upper tracing Effect of dialyzate of citrated plasma, after three-hour dialysis against Ringer-Locke solution Lower tracing Effect of citrated ox blood and of plasma obtained from it

The foregoing experiments seemed open to criticism because of the possibility of contamination by tissue juices or other substances which might have affected the behavior of the artery Use of laboratory animals made it possible so to regulate the conditions under which blood was withdrawn, that our scanty supply of herudin could be utilized This anticoagulant has the advantage that it does not reduce the sensitiveness of the arterial strip Accordingly, numerous experiments were done with blood of the dog The method used was as follows

Method Uncoagulated Blood of the Dog (Suggested by Dr M T Burrows)—Enough 4-ounce wide-mouth bottles, together with stirring rods and cannulas, were boiled in soapy water, washed, soaked in 33⅓ per cent hydrochloric acid to remove traces of alkali, left to wash at length under the tap, thoroughly washed with distilled water, dried, oiled, and left to drain The cannulas were made as large as could be forced into the artery They were about 1 foot long, and suitably bent to reach the bottom of the bottle, below the level of the anticoagulant solution The carotid artery was exposed and

wiped free of blood by means of a piece of oiled gauze, and further protected from blood by inserting beneath it a similar layer of gauze It was then nicked, and washed inside, first with paraffin oil, and then (in the later experiments) with strong citrate solution The blood was then allowed to flow rapidly to the desired volume, with constant stirring The anticoagulant solutions used were citrate, as in the experiments with blood of the ox, except that it was not neutralized, 1 per cent oxalate in 0 9 per cent salt solution, and herudin in Ringer-Locke solution The concentrations are indicated in the tables Certain modifications of method, such as neutralizing of the citrate solution, observation of sterile precautions, drawing of blood by syringe without anesthesia, use of excessive oxalate later to be reprecipitated, were tried, but did not appear advantageous For anesthetic, ether was gradually discarded in favor of paraldehyd, which seemed better for our purpose The order in which the tests were carried out was the same as that already described

TABLE 2—CITRATED DOG BLOOD

Experiment	Constriction	Citrate, Per Cent	Material Obtained	Remarks
98*	Trace	0 2	Same day	Small clot next day
98	+	0 2	Same day	Small clot next day
100	+	0 2	Same day	Artery not very active
100	+	0 3	Same day	Artery not very active
101	Trace	0 2	Same day	Artery not very active
113*	0 ?	0 3	1 day previous	Sensitive artery No effect in 2½ minutes
113	Trace	0 3	1 day previous	Sensitive artery
116	+	0 3	Same day	Clot ?
123	+	0 3	Same day	

* Brackets indicate more than one observation on same material

Results—Oxalated blood of the dog uniformly caused a constriction, which, though marked, was in no way comparable to that induced by defibrinated blood Citrated blood had a similar effect, though less marked and more variable Of seven properly controlled experiments, in which the citrated blood was substituted for citrated Ringer-Locke solution, all, as shown in Table 2, showed some increase of tonus varying from a trace to a moderate constriction The type of curve differs from that caused by defibrinated blood in that the sharp onset and the abrupt rise are replaced by a more or less prolonged latent period and a gradual rise

Herudinized blood of the dog was investigated in nine experiments, of which two were discarded because of gross clotting, two because of insensitive test objects The results were not uniform In Experiment 103, for example, as shown in Figure 3, substitution of herudinized blood for herudinized Ringer-Locke solution failed to cause a rise The latter solution, however, in itself caused a moderate rise, which may have obscured the results This was the only occasion in which

the herudin had any such effect The test object reacted vigorously to defibrinated blood in the presence of the same concentration of herudin, thus demonstrating its sensitiveness In two experiments the substitution of herudinized blood for herudinized Ringer-Locke solution resulted in no increase of tone for two and ten minutes, respec-

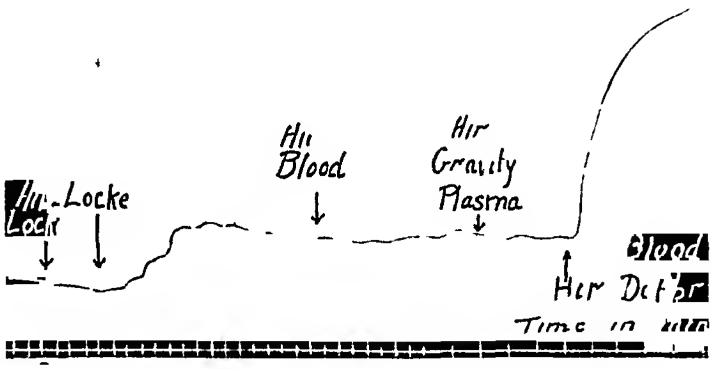

Fig 3—Experiment 103 Ox carotid Dog blood Effect of herudinized Ringer-Locke solution, herudinized blood, plasma obtained from same by gravity and defibrinated blood to which herudin had been added

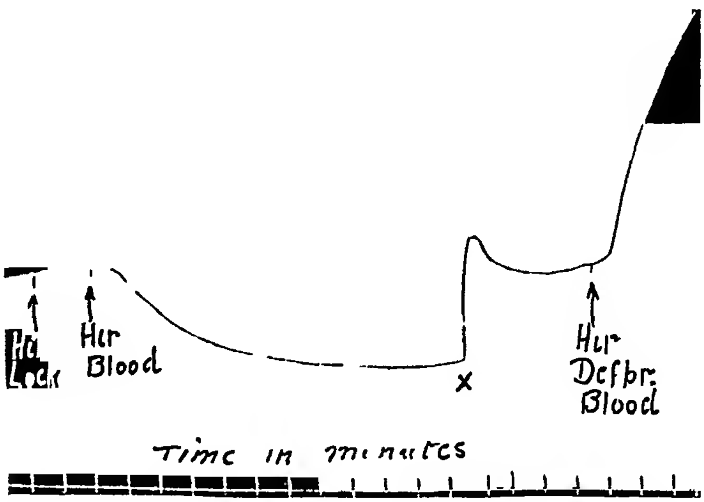

Fig 4—Experiment 104 Ox carotid Effect of herudinized blood of dog as compared to defibrinated blood to which herudin was added Note spontaneous contractions at X

tively, and then a sharp rise without any further manipulation Figure 4 shows the second of these The herudin blood caused a gradual relaxation lasting for ten minutes, at the end of which period a sharp spontaneous rise (X) occurred, followed by an incomplete fall The further development of the curve was interrupted for the purpose of testing the artery by the use of defibrinated blood to which a like amount of herudin had been added As far as it goes, however, this curve is precisely similar in form to rhythmic changes of tonus which

we have since frequently observed in arteries left undisturbed in Ringer-Locke solution containing no dextrose Certainly no other explanation is at hand for such a prodigious latent period Two other specimens of blood caused a rise, not explicable in this manner

DISCUSSION

The presence of a vasoconstrictor substance in many of the specimens of blood which had been withdrawn into anticoagulant solutions may be tentatively explained as follows After the blood leaves the circulation, and before it becomes thoroughly mixed with the anticoagulant solution, the blood platelets break down and liberate a vasoconstrictor substance That they break down with extreme ease has been shown by Deetjen[35] That when broken down they liberate a powerful vasoconstrictor substance is demonstrated later in this paper Coagulation of blood is accompanied both by elaboration of vasoconstrictor substance and breakdown of platelets That this breakdown is out of proportion to the amount of clot formed is shown by the fact that a very small clot is associated with a very marked vasoconstrictor action This observation was made by O'Connor[12] and Kahn,[26] and confirmed by the present work Thus, there is much indirect evidence that the foregoing explanation is correct We are therefore inclined to disregard those experiments in which a vasoconstriction occurred, and to emphasize those in which it was absent From this point of view, the results obtained with uncoagulated blood of the dog tend to substantiate those obtained with uncoagulated blood of the ox

Blood of the Calf—After the above conclusions were reached, a final experiment was performed on the blood of the calf This experiment seems worth a detailed description It was undertaken to obviate on the one hand the possibility of contamination as in the experiments on the blood of the ox, and on the other hand the uncertainties of using a blood foreign to the species from which the artery was obtained, as in the experiments on the blood of the dog In addition, it offered the advantage that herudin could be used The protocol follows

Experiment 164—Aug 16, 1917

12 30 p m Carotid arteries of the ox collected in cold Ringer-Locke solution about one hour previously, arrived at the laboratory

3 p m Calf, 4 days old, bled through an oiled cannula inserted into the carotid artery, according to the method used in obtaining blood from the dog The artery was washed out inside with citrate solution and oil before inserting the cannula All possible care was taken and no technical errors were detected The blood was obtained in two lots, one containing herudin (4 years old) in the proportion of 1 mg to 6 c c of blood, the other (a product obtained from C E Bischoff and Company about three months previously) in proportion of

35 Deetjen, H Ztschr f physiol Chem, 1909, **63,** 1

1 mg to 2 5 or 3 c c of blood The plasma was obtained by centrifugalization at 1,800 R P M for one-half hour for the tests with Arteries 1 and 2, for one hour for the tests with Arteries 3 and 4 One lot of blood, probably that containing the older herudin in weaker concentration, was found after one-half hour at 38 C to contain half a dozen small clots The other lot was free from clots

9 30 p m Beginning of tests The artery was then in Ringer-Locke solution containing dextrose but no sodium bicarbonate This fluid was replaced by Ringer-Locke solution containing herudin in the same proportion as the second specimen of blood, 1 mg to 2 5 c c The concentration of herudin in the control solution was therefore equal to or greater than that of the blood tested The herudinized Ringer-Locke solution was then replaced by herudinized blood, this by herudinized plasma Finally the artery was tested by means of defibrinated blood

Results —The results are shown in Figure 5 Neither the herudinized Ringer-Locke solution, the herudinized blood nor the herudinized plasma had the slightest effect on the artery Indeed, the tonus

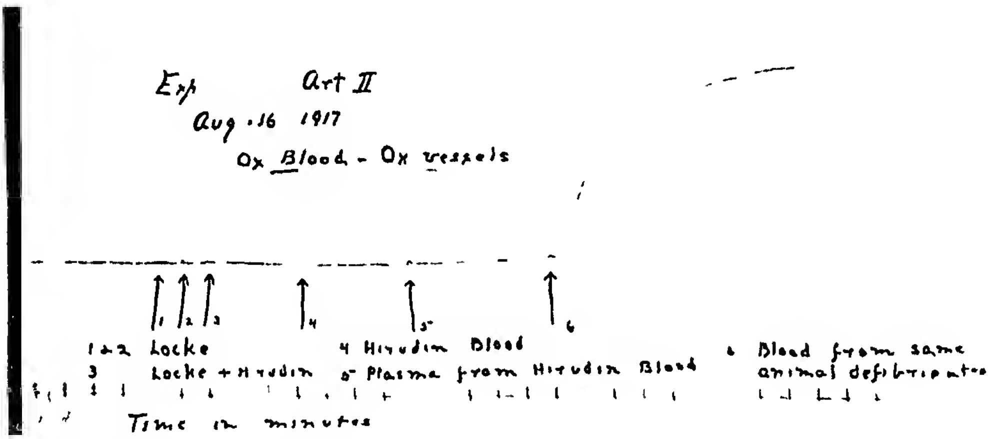

Fig 5—Experiment 164 Ox carotid Calf blood Effect of herudinized blood and plasma containing no clot Order of tests (1) and (2) Ringer-Locke solution, (3) same with herudin, (4) herudinized blood, (5) Plasma from herudinized blood, (6) blood from same animal defibrinated

remained so constant that it was suspected that the artery was dead By the use of defibrinated blood, however, a sharp characteristic rise resulted, thus proving the sensitiveness of the preparation The blood was in contact with the preparation without effect for four minutes, the plasma for five minutes A second preparation treated with the same materials in the same order gave the same results In this case the blood was in contact with the preparation for eight minutes, and the plasma for seven minutes The response to defibrinated blood was even more marked in this test than in the previous one The blood and plasma contained no clot In contrast to the foregoing are the results shown in Figure 6 Here substitution of herudinized blood for herudinized Ringer-Locke solution caused very moderate slow rise On replacing the blood with herudinized plasma the rise continued,

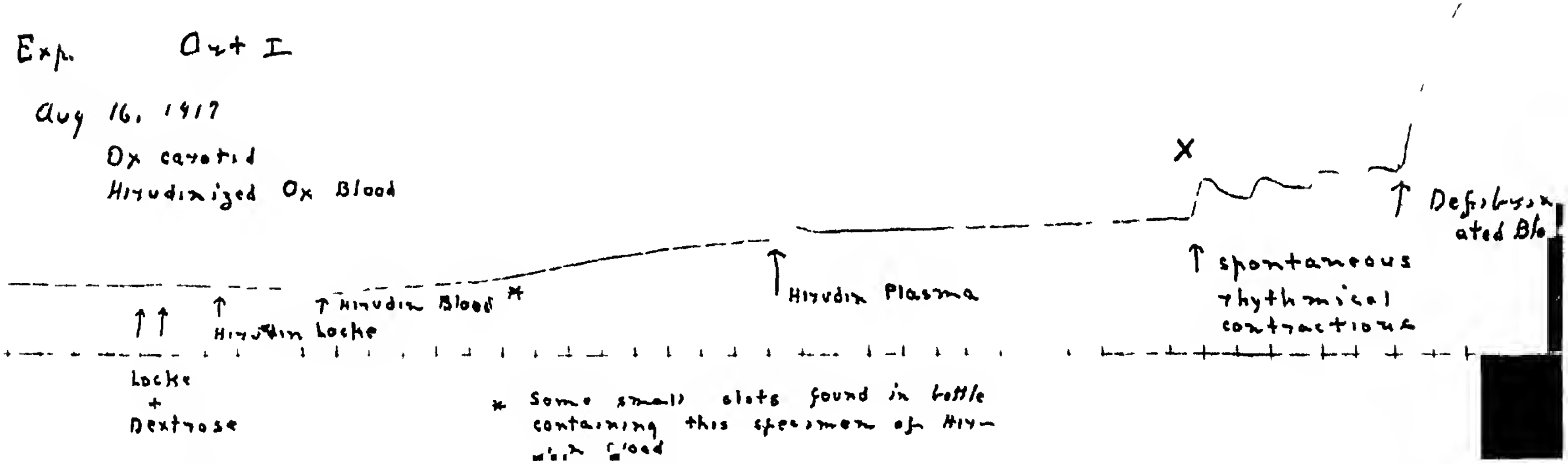

Fig 6—Experiment 164 continued Ox carotid Calf Blood Effect of herudinized blood containing clot, and of plasma obtained from it Order of tests (1) and (2) Ringer-Locke solution, (3) herudinized Locke solution, (4) herudinized blood in which some small clots were found, (5) herudinized plasma, (6) defibrinated blood Note spontaneous contractions at X

and later spontaneous rhythmic contractions developed The blood in this case contained several small clots In this experiment, then, blood in which clotting had been entirely prevented had no effect on the artery of the same species, whereas blood in which a small amount of clotting had taken place caused a definite increase of tonus

To summarize the results obtained with uncoagulated blood

Citrated blood of the ox as obtained in the slaughter house had no constricting effect on the excised ox artery Blood of the dog obtained by a method which was less open to criticism had a variable amount of vasoconstrictor action, less in the case of the citrated blood than in the case of the oxalated blood, and nil over a relatively long period in three out of five experiments with herudinized blood As the latter experiments were not unequivocal, a final experiment was made with blood of the calf, with a clear-cut result that, provided it had been prevented from clotting, it had not the slightest effect on the excised artery It seems safe to conclude, therefore, that there is no vasoconstrictor substance in the normal circulating blood of animals

Blood Platelets—These were obtained according to the method of differential centrifuging first suggested by Mosen[36] and described by Bayne-Jones[37] and Lee and Vincent,[38] by which advantage is taken of the relatively low specific gravity of the platelets

Method—Ox blood centrifuged at 1,500 to 1,800 R P M for from a half to three quarters of an hour was found to separate into two approximately equal layers, sediment and plasma This plasma was aspirated and centrifuged at 3,000 R P M for periods of about five minutes, each time the supernatant fluid was decanted and centrifuged afresh By repeating this process three or four times a sediment was obtained in which at most two or three cells per high-power field could be detected by microscopic examination of the fresh specimen The scanty platelet sediment thus obtained, though cohesive, could be emulsified by the use of a capillary pipet, and washed, first, in 0 9 per cent saline, and finally in Ringer-Locke solution After two or three washings it was shaken vigorously by hand with glass beads and distilled water, and a volume of double-strength Ringer-Locke solution equal to that of distilled water was added Out of nearly a liter of citrated blood of the ox a thin film of pure platelet was obtainable, in volume a small fraction of a cubic centimeter

Five experiments were performed with pure ox platelets, a great number with less pure platelets of ox, and one each with platelets of dog and pig

Results—The results were constant and very striking The effect of the platelet extract is to cause an abrupt rise of the writing-point, which rapidly gathers momentum and continues to rise at a rapid rate until the maximum effort of the artery is expended This is indicated by the change in shape of the strip, long and attenuated, before the constriction, short and contracted afterward The effect was even

36 Mosen, R Arch f Anat u Physiol, Physiol Abt, 1893, p 352

37 Bayne-Jones, S Am Jour Physiol, 1912, **30,** 74

38 Lee, R I, and Vincent, B The Archives Int Med, 1914, **13,** 398

more striking than that occasioned by serum or defibrinated blood Even an extract from a film of platelets at the bottom of a centrifuge tube, so thin as to be scarcely visible, caused a constriction comparable to that of defibrinated blood Once contracted, the vessel remained so until treated with nitrite in a manner to be described The effect is shown in Figure 8 at (3) The abrupt onset, the rapid rise, and the wide latitude of the constriction, comprising almost the entire width of the drum, are well shown Perhaps the activity of the platelets is best indicated in Figure 11, which demonstrates the effect of a dried preparation of platelets diluted 1 100,000 in Ringer-Locke solution This preparation was obtained by boiling the platelet extract in slightly acid medium and drying the filtrate With only a single exception, easily explicable on technical grounds, the platelet extract caused this very striking constriction of the excised artery We were also able to confirm Stewart's[39] observations that the platelet extract causes constriction when injected into the interior of a long piece of artery without coming into contact with the cut surface of the vessel

Erythrocytes—In order to free the red corpuscles from platelets, advantage was taken of the low specific gravity of the latter, on the assumption that slow centrifuging through large quantities of fluid would leave the platelets in suspension

Method—Accordingly, from 10 to 50 c c of citrated blood were poured on top of 0 9 per cent salt solution in 50 c c centrifuge tubes and centrifuged at slow speed for periods of about ten minutes The speed was such as to require about one hour for separation of ox blood into equal quantities of plasma and sediment The washing fluid was usually 0 9 per cent sodium chlorid Solution of greater specific gravity, such as 2 7 sodium chlorid and 10 per cent commercial dextrose, were tried and seemed to offer no advantage, nor did preliminary sedimentation by gravity through a large quantity of fluid After centrifuging, the supernatant fluid was decanted and the sediment poured into a tube of fresh solution This process was repeated at least four times, the washed corpuscles were examined microscopically by means of Wilson's stain in three experiments In one, occasional large clumps of platelets, in a second, no typical platelets whatever, in a third only rare ones, were seen The number of platelets was, therefore, at least very much diminished The strongest concentration of red corpuscles tested was a 1 3 dilution of a suspension so dense as to be indistinguishable from blood The cells were laked by shaking with distilled water and glass beads, and brought to physiologic strength by adding a volume of double strength Ringer-Locke solution equal to the distilled water A similar mixture of distilled water and double strength Ringer-Locke solution was applied to the artery immediately before the test as a control In all, seven specimens of red blood corpuscles were examined and the arteries were found to be active in all experiments

The results are shown in Table 3 In only one experiment, the first, was there more than a slight increase of tone In this a sharp rise inaugurated a series of rhythmic contractions associated with

39 Stewart, G N Arch. d mal du coeur, 1914, **7**, 454

TABLE 3—Red Corpuscles Shaken with Water + Double Locke

Experiment*	Constriction	Concentration†	Material Obtained	Remarks
51	++	Thin	1 day previous	Latent rhythm with increased tonus
60	0	1 50	2 days previous	
62	0	Rather thin	1 day previous	
63	0	Dense	Same day	
65	Trace	Medium	1 day previous	Rhythmic contractions with very slight increase of tonus
82	+	Dense	Same day	Belated moderate rise associated with rhythmic contractions
91	0	1 3	Same day	

* The first five experiments were performed with ox corpuscles, the remainder with dog corpuscles

† Under concentration is indicated the degree of dilution of the corpuscles before testing

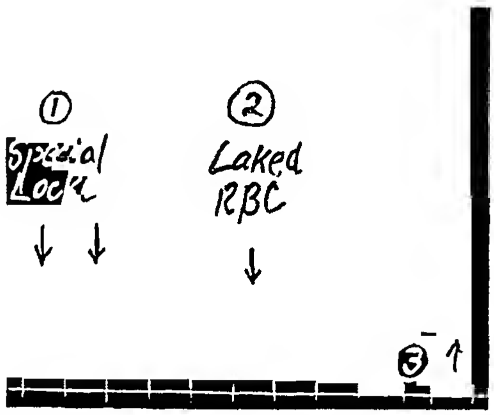

Fig 7—Experiment 91 Ox carotid Dog blood Order of tests (1) water and an equal volume of double Locke solution, (2) laked red corpuscles restored to tonicity by means of double strength Ringer-Locke solution, (3) defibrinated blood

increasing tone, a phenomenon precisely similar to that observed later in a number of instances in arteries left undisturbed in Ringer-Locke solution The same phenomenon, though much less marked, occurred in Experiment 82 after a latent period of several minutes In Figure 7 is shown the absence of effect of laked corpuscles of dog in a dilution equal to one-third of a very dense suspension, as compared to the very marked vasoconstrictor effect of defibrinated blood The results are consistent, red corpuscles of dog or ox, laked or in suspension, have no effect on the excised artery other than a tendency to rouse its latent rhythmicity The objection might be raised that a vasoconstrictor substance diffused out of the corpuscles during the washing If so, it should diffuse out into the circulating blood and render the latter more active than it actually is Moreover, platelets which were treated in a similar way, except that the centrifuging was necessarily faster, remained active after repeated washings

Leukocytes.—The method followed was essentially that of Zinsser.[40]

Method.—Four dogs were injected, in all instances with a 5 per cent suspension of aleuronat in bouillon or distilled water, containing 3 per cent of soluble starch. The water appeared better, if anything, than the bouillon. From 10 to 20 c.c. of this mixture were injected into the pleural cavity in the lower axilla, under sterile precautions. After a period varying from one to nine days, the animal was killed by bleeding. This permitted opening of the pleural cavity without contamination with blood. The exudate was withdrawn by means of an oiled 50 c.c. pipet. The contents of one pleural cavity were divided into two parts, the first being tested unmodified, the second, after treatment with distilled water and double strength Ringer-Locke solution in exactly the way described for the blood platelets. The contents of the other pleural cavity were mixed with strong citrate or oxalate solution and centrifuged. The cells were washed three times in 0.9 per cent. sodium chlorid and once or twice in Ringer-Locke solution. The final sediment was shaken with distilled water and restored to tonicity with double strength Ringer-Locke solution in exactly the way described for the platelets. Smears of the original exudate stained by Wilson's stain showed no platelets whatever, nor did platelet counts, according to the method of Wright and Kinnicutt,[41] very kindly performed for us by Dr. Hirose. An examination of a smear taken from the top of the first sediment after rapid centrifuging also failed to demonstrate platelets. Red corpuscles were present in the first specimens in numbers about equal to the leukocytes, but became much less prevalent in later specimens, so that the sediment had a chalky red appearance. The final specimen contained none. It should be noted that, in a preliminary experiment, aleuronat failed to affect the artery in concentration of 10 per cent.

TABLE 4.—White Blood Cell Pleural Exudate of Dog

Experiment	Constriction	Concentration*	Red Blood Corpuscles†	Platelets	Remarks
Part 1					
116	0	1:1	++	0	Exudate untreated
123	Trace	1:1	+	0	Exudate untreated
127	0	1:1	+	0	Exudate untreated
Part 2					
116	++	1:5	++	0	Exudate + H_2O + double Locke
123	+—	1:5	+	0	Exudate + H_2O + double Locke
127	0	1:5	+	0	Exudate + H_2O + double Locke
Part 3					
116	+	1:20	++	0	Washed sed. + H_2O + double Locke
117	—	1:20	++	0	Washed sed. + H_2O + double Locke
123	0	1:20	+	0	Washed sed. + H_2O + double Locke
127	0	1:8	0	0	Washed sed. + H_2O + double Locke

* Under concentration is indicated the degree of dilution of the material before testing.
† Under red blood corpuscles is indicated the extent to which red corpuscles were present in the material.

40. Zinsser, H.: Infection and Resistance, The MacMillan Co., New York, 1914.

41. Wright, J. H., and Kinnicutt, R.: Jour. Am. Med. Assn., 1911, **56**, 1457.

Results—In all, seven pleural exudates, taken from the four dogs, were examined The results are shown in Table 4 Part 1 shows the effect on the ox artery of the exudate untreated, Part 2, that of exudate treated with water and double strength Ringer-Locke, Part 3, that of washed sediment similarly treated The greatest constriction observed with untreated exudate was a trace The modified exudate caused a marked constriction in one instance, inconsistent results in a second, and no effect in a third The washed and treated sediment caused a moderate constriction in the first experiment only, in the other three, no effect or slight loss of tonus

Although the absence of platelets from all specimens was demonstrated, the absence of broken-down products of platelets was not, since the latter might have been in solution or in a form not recognizable under the microscope This is especially likely in those specimens which were found to contain blood Indeed, it is difficult to conceive in what manner erythrocytes could enter a cavity inaccessible to the platelets, which are not only smaller than the red cells, but also, unlike them, possess the power of independent motion (Deetjen[42]) In the successive experiments the number of red cells diminished, and with it the vasoconstrictor power of the exudate For these reasons we are inclined to emphasize the results of the last experiment, No 127, on an exudate which was free of red cells This experiment will therefore be described at length

Experiment 127—Nine days previous to this experiment 20 c c of a 5 per cent aleuronat suspension in 3 per cent aqueous solution of soluble starch were injected into each pleural cavity of a dog On the day of the experiment the animal was killed by bleeding, and the exudate immediately removed with an oiled pipet The exudate from the right cavity was centrifuged and washed as already described, the final volume of the compact sediment being 1 25 c c This was treated with 5 c c water and 5 c c double Ringer-Locke solution, the resulting dilution being 1 8 The effect is shown in Figure 8 to be nil while 0 6 c c of platelet sediment of dog treated in the same way as the washed exudate and with the same amounts, caused a maximal constriction That is, 1 25 c c of exudate had no effect, whereas half as much platelet sediment caused a maximal constriction Smears and counts failed to demonstrate any platelets The differential count of the original exudate gave the following percentages

Mononuclear basophils	1 per cent
Endothelial cells	4 per cent
Polymorphonuclear leukocytes	95 per cent

One red corpuscle was found after prolonged search

The tabulated results, in conjunction with the foregoing experiment, seem to justify the conclusion that the cells of the pleural exudate of the dog, in contrast to platelets, cause no constriction of the ox artery How far this is applicable to the cells of the blood is

42 Deetjen, H Arch f path Anat 1901 **164,** 239

not manifest Leukocytes of exudates are said to differ morphologically from those of the blood, yet it is obvious that the former can arise only from the blood, assuming that they do not proliferate in the pleural cavity, an unlikely event, which we have not investigated In any case, no other method of obtaining platelet-free leukocytes in bulk is at hand, apart from the examination of lymph nodes and other organs— a method even more indirect

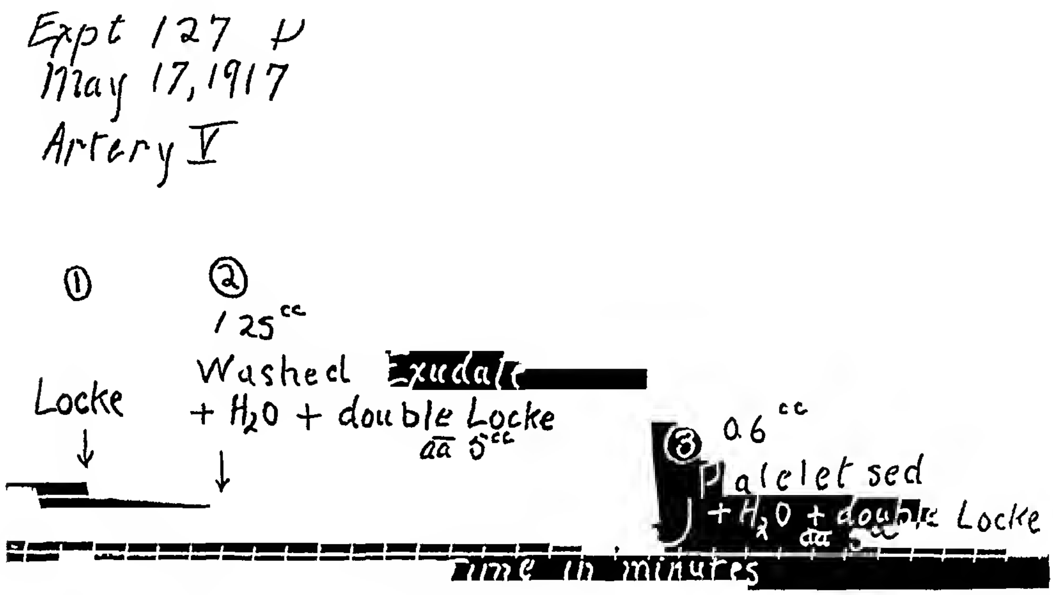

Fig 8—Experiment 127 Effect of leukocytes obtained from pleural exudate of dog on ox artery, as compared with effect of dog platelets Order of tests (1) Ringer-Locke solution, (2) 1 25 c c washed exudate, plus 5 c c water, plus 5 c c double Locke solution, (3) 0 6 c c platelet sediment plus 5 c c water plus 5 c c double Locke solution

Tissue Extracts—

Lymph Nodes—Eight or ten lymph nodes were obtained from an ox, slaughtered by bleeding, on the day of the experiment They were freed from fat, chopped, washed once with Ringer-Locke solution, and ground in a mortar with Kahlbaum's washed sand, to which 50 c c of Ringer-Locke solution was added The resulting emulsion was light brown The pieces of tissue were fairly large, and in spite of the washing it is certain that not all of the blood was removed In a second experiment the parts of the lymph nodes in which blood was visible were cut away The remainder appeared free from blood, but the final emulsion was yellowish

Results—In both experiments the extract of lymph node caused a vasoconstriction only slightly exceeded by the effect of defibrinated blood

Other Organs Similar extracts of spleen, bone marrow, and thymus failed to cause a constriction The results are difficult to interpret, owing to the complex nature of any organ, together with the difficulty of eliminating the blood Possibly the cause of the dif-

ference between lymph node and pleural exudate is that the former consists mainly of lymphocytes, the latter of polymorphonuclear leukocytes It may be mentioned that in a single experiment the lymph of dog gave a marked vasoconstrictor effect, attributed at the time to contamination with blood Sufficient basis for interpreting the results, however, is lacking

Plasma—It was to plasma rather than uncoagulated blood that our attention, like that of most previous workers, was first directed, on the assumption that the effect of the two is identical

Method—The plasma was prepared from each of the various kinds of uncoagulated blood mentioned in the section headed "uncoagulated blood," where the method of obtaining the blood has also been described in full Separation of the plasma from the corpuscles was effected in the earlier experiments by prolonged centrifuging at a speed of 3,000 revolutions per minute, with the idea of getting rid of the blood platelets As this degree of force was later thought to favor the breakdown of blood platelets, it was reduced, first to a period varying from one-half to one hour at 1,800 R P M, later to several hours at very slow speed, and finally to sedimentation under gravity alone, usually overnight Blood of the ox unfortunately failed to sediment in this manner, but blood of the dog separated very readily In most of the experiments the centrifuge tubes were oiled or paraffined, this did not, however, seem to offer any advantage over thorough cleaning In the attempt to obtain a plasma free from vasoconstrictor substance various sorts were investigated, among them citrated plasma of the ox and citrated, oxalated and herudinized plasma of the dog Plasma of the hen, which had the advantage that it could be prepared without the use of an anticoagulant, simply by keeping the blood cold, was tried on two occasions Finally a single experiment was made on the plasma of the calf

In the earlier experiments plasma was compared to Ringer-Locke solution containing the same amount of anticoagulant In these herudin was not used Later, when it became evident that the process of preparing the plasma might not be devoid of effect on its activity, it was compared with the uncoagulated blood from which it was obtained This group of experiments included those on herudinized plasma, and embodied all the technical improvements in the manner of drawing the blood which we could devise This method has already been described

Results—As might be expected, plasma prepared from the type of uncoagulated blood which has been shown to be active, was also active Citrated and oxalated plasma of the ox and of the dog, when substituted for Ringer-Locke solution containing the same amount of anticoagulant, caused always some increase of tonus An example is shown in Figure 2 This constriction varied in degree in a seemingly capricious manner from a trace to a well-marked rise The curves were characterized by the same latent period and gradual onset which were noted in the case of the active specimens of uncoagulated blood Exchange of plasma for defibrinated blood to which the same amount of anticoagulant had been added resulted almost invariably in a further rise, usually twice to several times the original It is interesting that plasma of the hen caused a very striking vasoconstriction,

though it is well known that the blood of the hen contains no cells morphologically similar to blood platelets Plasma of the above types when substituted for Ringer-Locke solution caused a vasoconstriction

The results of experiments in which the plasma was substituted for the uncoagulated blood from which it was prepared are shown in Table 5, which has been arranged according to the anticoagulant used In the experiments in which citrate or oxalate plasma was investigated, a definite increase of tonus resulted when plasma was substituted for uncoagulated blood In the four experiments on herudinized plasma

TABLE 5—EFFECT OF SUBSTITUTING PLASMA FOR THE BLOOD FROM WHICH IT WAS PREPARED

Experiment	Constriction	Anticoagulant	Concentration of Anticoagulant	Method of Separation
61	++	Citrate	0 5%	Rapid centrifugalization
66	+++	Citrate	0 5%	Slow centrifugalization for 5 hours
103	+	Citrate	0 2%	Gravity + centrifugalization for 1 hour at low speed
108*	Trace	Citrate	0 3%	Gravity
113	++	Citrate	0 3%	Gravity
147	++	Citrate	0 3%	Gravity
93	Continued rise	Oxalate	0 1%	Centrifugalization for 25 minutes at 1,800 R P M
113	Trace	Oxalate	0 05%	Gravity
87	+	Herudin	1 3,300	Centrifugalization for 80 minutes at 1,800 R P M
103	0	Herudin	1 3,300	Gravity
105-B IV	0	Herudin	1 3,300	Centrifugalization 45 minutes at 1,800 R P M and 45 minutes at 3,000 R P M
105-B† V	+	Herudin	1 3,000	Centrifugalization 45 minutes at 1,800 R P M and 45 minutes at 3,000 R P M
164	0	Herudin	?	Centrifugalization 1 hour at 1,800 R P M

* Not very sensitive artery
† Plasma drawn from a level near the platelet layers
Experiments 61, 66 and 147 on blood of the ox, the remainder on blood of the dog

in which this comparison was made, in one, Experiment 87, the plasma had more vasoconstrictor effect than the blood In this case only was the blood in itself active during the period of observation In Experiment 105 the plasma drawn from the top of a centrifuge tube caused no constriction, whereas that drawn from a point near the platelet layer did cause a constriction In the other two experiments no increase of tonus resulted when plasma was substituted for herudinized blood The first of these is shown in Figure 3 already referred to, in which neither the blood, by replacing herudinized Ringer-Locke

solution, nor plasma by replacing blood, caused any change of tonus in the arterial strip, although the activity of the preparation in defibrinated blood was well marked

The fourth experiment on herudinized plasma was Experiment 164 performed on herudinized blood of the calf, and has been described at length under the heading "Uncoagulated blood" In Figure 5 it will be noted that, on substituting the herudinized plasma for the herudinized blood from which it was made, no change of tonus whatever was discernible The preparation then demonstrated its sensitiveness in the presence of defibrinated blood

To sum up If a specimen of uncoagulated blood causes a constriction when substituted for Ringer-Locke solution, the plasma prepared from it has the same effect If, then, plasma from citrated or oxalated blood is compared with uncoagulated blood from which it was prepared, a constriction results If this same comparison is instituted in the case of herudinized plasma of the dog, the results are variable, but in at least one, and probably two, instances out of three no vasoconstriction resulted In the experiment on the calf the herudinized plasma, when substituted for the herudinized blood from which it was prepared, had absolutely no effect

Attempts were made to explain the frequent difference in effect between plasma and uncoagulated blood Violent and prolonged shaking of the latter failed to increase its vasoconstrictor effect Comparison between plasma and sediment failed in three properly controlled experiments to show any difference The most promising way of testing the effect of centrifuging was cut short by the close of work, not, however, before three experiments had been performed This method consisted in comparing blood, which had been centrifuged and stirred, with the original blood One experiment showed no increase, a second a slight increase, and a third a marked increase in vasoconstrictor power after this treatment Further experiments were made to exclude other possible causes of the vasoconstrictor action of plasma The suggestion was made that the hydrogen-ion concentration was sufficiently altered by the current of oxygen to cause a change of tonus in the artery, and, in fact, the P^{H} was found by the method of Levy and Marriott[34] to change from 7 25 to 7 45 under oxygenation This change is much less than that needed to produce a reaction in the artery, and could be prevented by bubbling human alveolar air through the plasma along with the oxygen Under these conditions the plasma reaction occurred nevertheless It also occurred, though naturally diminished, in the absence of a current of oxygen The effect of change of hydrogen-ion concentration, therefore, is excluded As to the nature of the vasoconstrictor substance which sometimes appears in plasma, it is plausible to assume its identity with that of serum

For evidence we can only offer the observation, several times repeated, that it passes readily through a celloid membrane (Fig 2)

Discussion —If circulating blood is not vasoconstrictor, it is unlikely that the circulating plasma is Such an event could be explained only on two grounds, either that the blood contains two antagonistic substances, vasoconstrictor and vasodilator, the one in the plasma, the other in the sediment, or that the blood represents a dilution of plasma by means of the inactive cellular (nonplatelet) elements In either case the sediment should be less active than the plasma Simpler and more probable is the explanation that centrifuging is by itself sufficient to cause elaboration of a vasoconstrictor substance, most likely by breakdown of platelets The failure of mechanical shaking to cause this breakdown might be explained on the ground that the intervening red corpuscles prevented the agglutination of platelets which ordinarily precedes their breakdown The failure to demonstrate a difference in the effect between sediment and plasma, and the occasional increase of vasoconstrictor effect as a result of centrifuging and remixing, afford some evidence that the explanation offered is the correct one, namely, that centrifuging causes an elaboration of vasoconstrictor substance Very much stronger evidence is offered by the fact that it is possible, by technical improvements and by the use of herudin, to obtain a plasma which, like the blood from which it is prepared, is totally inactive, and in which, consequently, neither the separation of the blood into plasma and sediment nor the mechanical effect of centrifuging can have any influence The conclusion seems justified, therefore, that the circulating plasma has no effect on the excised strip of ox artery

PART III

CERTAIN PROPERTIES OF THE VASOCONSTRICTOR SUBSTANCE

Certain physiologic and chemical properties of the vasoconstrictor substance were studied its effect on the carotid and coronary arteries of the ox, and its relation to heat, precipitation of proteins, dialysis and extraction with various fluids

Method of Preparation of the Vasoconstrictor Substance—Blood platelets unmixed with other cells were isolated from the blood of the ox in the manner already described Enough sediment for the experiments on physiologic effect, heat and dialysis could be obtained in this way They were treated with distilled water and double strength Ringer-Locke solution as usual When larger bulk was required, centrifuging for purposes of purification proved too wasteful Accordingly, a simpler method was used Two liters of citrated blood were centrifuged for about thirty minutes at 1,800 R P M The cloudy plasma was aspirated and centrifuged for about thirty minutes at 3,000 R P M The resulting plasma was removed by aspiration The sediment consisted of a gummy white mass discolored with erythrocytes and containing a small

amount of plasma It was treated in one of two ways It was shaken with 50 c c of distilled water, washed into a beaker and brought to a boil Dilute hydrochloric acid was added drop by drop until a flocculent precipitate appeared This precipitate was filtered off and washed with distilled water The filtrate and washings were dried over a steam bath The dried product was accumulated and kept in desiccator From 10 liters of citrated blood about 1 gm of the dried product was obtainable Between 0 1 and 1 0 gm of this dried substance was used for extraction That this amount was more than ample is shown by the fact that the substance was capable of causing an extreme constriction in a dilution of 1 100,000, that is, for the 5 c c volume needed for the physiologic tests, only 0 00005 gm of the substance was required Extraction consisted simply in stirring the finely divided dried substance in an evaporating dish by hand at room temperature The extract was filtered off and the residue washed repeatedly with the extractive The filtrate was dried on the steam bath The filter paper and residue were spread out on the electric stove and allowed to dry until no further odor of the extractive could be detected To both extract and residue distilled water was added and subsequently a volume of Ringer-Locke solution equal to that of the water

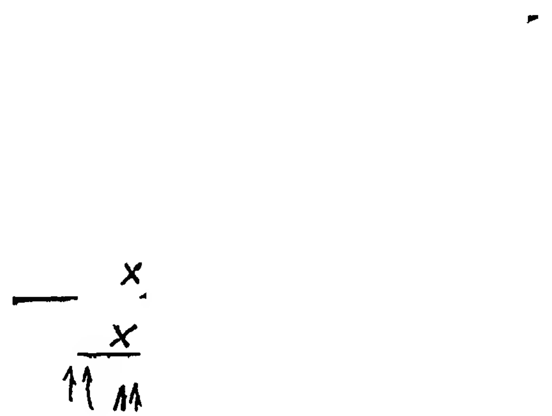

Fig 9—Experiment 33—Upper tracing Ox carotid Lower tracing Ox coronary Two rings Lifting weight, 10 gm Stretching weight, 20 gm At X, Ringer-Locke solution replaced by aqueous extract of pure platelets of ox, restored to tonicity by the addition of double strength Ringer-Locke solution

The other method consisted in mixing the platelet sediment with plaster-of-Paris After the mass had set, it was ground up and extracted by means of the Soxhlet apparatus Control extractions of plaster-of-Paris yielded no vasoconstrictor substance Each individual extract represented all the platelets obtainable from not less than 250 c c of blood, usually about 500 c c of blood In one experiment, No 84, platelets of the pig were used, in all the others, platelets of the ox The manner and duration of the extraction are indicated in the tables Extracts were taken up with distilled water and double strength Ringer-Locke solution added Other methods will be described as they come up

Physiologic Action—The constrictor action of platelet extract on the carotid artery has already been described Its action on the excised coronary artery was observed in two experiments

Method—For this purpose rings were cut from the coronary artery of a fresh ox heart They were not cut open, but were tied together and suspended in Ringer-Locke solution In Experiment 33 two rings were used, the stretching weight was 20 gm, and the lifting weight 10 gm In Experiment 145 smaller

rings were used and the weights were 10 and 6 gm, respectively The material for the first experiment was obtained from pure platelets, that of the second from platelets containing an admixture of red cells

Results—The effect of the platelet substance on the carotid and coronary arteries is shown in Figure 9, Experiment 33 An immediate well marked contraction of both preparations resulted In Experiment 145 the effect on the coronary artery was the same Epinephrin, on the other hand, in a concentration of 1 50,000, subsequently caused a sharp relaxation of the same preparation

Discussion—The fact that the platelet substance causes a constriction of the coronary artery of the ox, whereas epinephrin, as is well known,[43] causes a relaxation, is strong evidence that the vasoconstrictor substance of platelets is not epinephrin Blood serum has been shown to have this constrictor effect on the coronary artery of the ox[1] The similarity of blood serum and platelet substance in this respect substantiates the conclusion stated, that the vasoconstrictor substance of clotted blood is derived from the platelets

Resistance to Heat—

Method—To determine the resistance of the platelet substance or of defibrinated blood to heat, they were boiled A solution of pure platelet substance in Ringer-Locke's fluid was heated until it boiled vigorously Again, pure platelets in 50 c c of distilled water containing 1 c c of 3 per cent acetic acid were boiled for five minutes, then evaporated to dryness over the steam-bath and extracted with 5 c c of Ringer-Locke solution Defibrinated blood was also brought to a boil and filtered Moreover, the ordinary process by which the platelet substance was prepared for many of the extraction experiments involved boiling and drying over the steam bath On other occasions the drying was continued over night, with the result that the remainder was partially carbonized The products were extracted with Ringer-Locke solution, where necessary, and tested by means of the arterial strip

Results—The boiled solutions of pure platelets both caused a vigorous constriction of a pair of arterial strips, that which was boiled the longer causing a maximal constriction The filtrate of boiled defibrinated blood caused a maximal constriction in a dilution of 1 4 The dried heat-acid filtrate caused invariably very marked constrictions, usually maximal, and in a dilution as high as 1 1,000,000 (Fig 11) All specimens of partially carbonized platelet substance caused vigorous constrictions

Discussion—That the vasoconstrictor substance both of platelets and of defibrinated blood resists heat substantiates to some degree the conclusion already reached, that its origin is the same The possibility that the platelet substance is epinephrin is not thereby excluded, as the behavior of the latter under the conditions described was not investigated The results are not inconsistent, however, with the inference

43 Park, E A Jour Exper Med, 1912, **16,** 532

drawn by physiologic methods, that the vasoconstrictor substance from platelets is not epinephrin

Relation to Proteins—Precipitation by Heat and Acid

Method—The platelet sediment of about 1 liter of citrated ox blood was mixed with distilled water and precipitated by heat and acid The precipitate was caught on a filter, drained, extracted with 5 c c distilled water and restored to tonicity by means of 5 c c of double strength Ringer-Locke solution Its effect on the excised artery was then observed in comparison with that of blood serum

Results—The effect of the heat-acid precipitate on the excised artery strip is shown in Figure 10, Experiment 81 A constriction resulted, which, though immediate and marked, was far from maximal, as was shown by substituting blood serum for the precipitate This

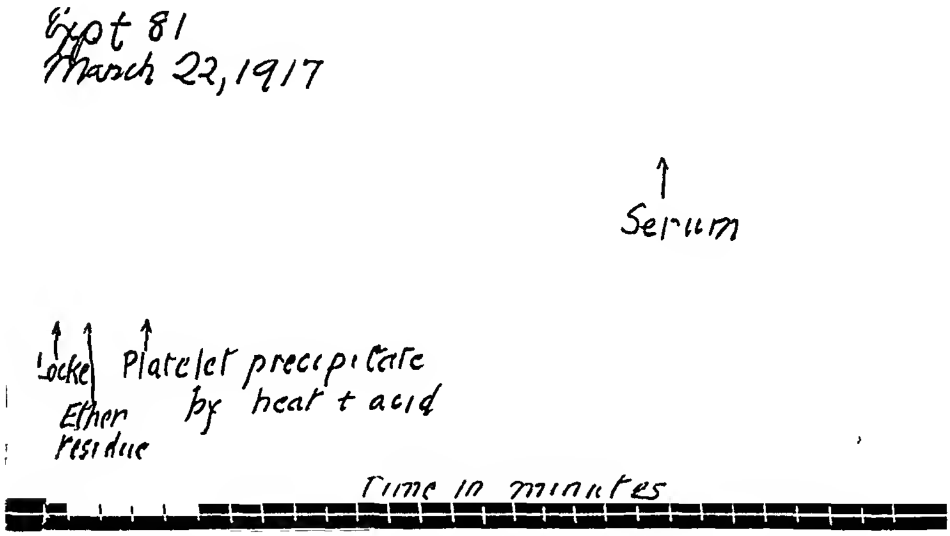

Fig 10—Experiment 81 Ox carotid Ox platelets Effect of portion of platelet extract coagulable by heat and dilute hydrochloric acid, as compared with effect of ox serum Ether residue—remainder after evaporation of 50 c c ether

resulted in a further constriction almost equal to the original This moderate constriction caused by the heat-acid precipitate contrasts strongly with that caused by the dried filtrate obtained by the same process The latter caused invariably an extreme constriction in numerous experiments, and in a dilution as high as 1 100,000 (Fig 11)

Discussion—The activity of the dried filtrate indicates that the vasoconstrictor substance is not precipitated by heat and acid That the precipitate had any vasoconstrictor action at all might easily be explained on the ground that some of the vasoconstrictor substance was caught mechanically in the flocculent precipitate

Dialysis—Celloidin membranes were used in all cases An active dialyzate in Experiment 36 gave several negative tests for protein Dialysis was carried on in the refrigerator

Method—The material dialyzed was (1) defibrinated blood and (2) pure platelets treated with distilled water and double strength Ringer-Locke solution These were dialyzed against Ringer-Locke solution in proportions to be indicated Three experiments were performed on defibrinated blood In the third, No 109, an attempt was made to rid the defibrinated blood of vasoconstrictor substance To this end 20 c c were dialyzed against 200 c c of Ringer-Locke solution, the dialyzate being changed three times at half-hour intervals, and the dialysis then continued over night, the total duration of the dialysis being twenty hours The dialyzator was then compared with the

Fig 11—Experiment 75 Ox carotid Ox platelets Effect of portion of platelet extract not coagulated by heat and dilute hydrochloric acid Filtrate dried and diluted 1 100,000

original defibrinated blood as to its vasoconstrictor activity One experiment, No 40, was performed on a solution of pure platelet substance, 20 c c of which were dialyzed against an equal volume of Ringer-Locke solution for twenty hours The dialyzate was removed and tested, and then replaced by fresh Ringer-Locke solution This exchange was repeated at fifteen-minute intervals, five times in all, and the dialyzator remaining in the membrane was tested for vasoconstrictor action

Results—The vasoconstrictor substance both of defibrinated blood and of platelets passed through the celloidin membrane very readily In Experiment 36 a nine-hour dialyzate of 200 c c of defibrinated blood against 50 c c of Ringer-Locke solution caused a maximal constriction In Experiment 38 a dialyzate of defibrinated blood caused a maximal constriction after only thirty-five minutes In Experiment

109 dialysis of defibrinated blood against repeated changes of Ringer-Locke solution so far reduced the activity of the dialyzator that it became only about a third as active as the original defibrinated blood The effect of the twenty-hour dialyzate of platelet substance is shown in Figure 12, Experiment 40 A marked vasoconstriction resulted Five subsequent changes of the dialyzate for fresh Ringer-Locke solution had the result that the dialyzator was rendered totally inactive

Discussion—The vasoconstrictor substance both of defibrinated blood and of platelet passes readily through a celloidin membrane The former can be almost completely, the latter completely, removed

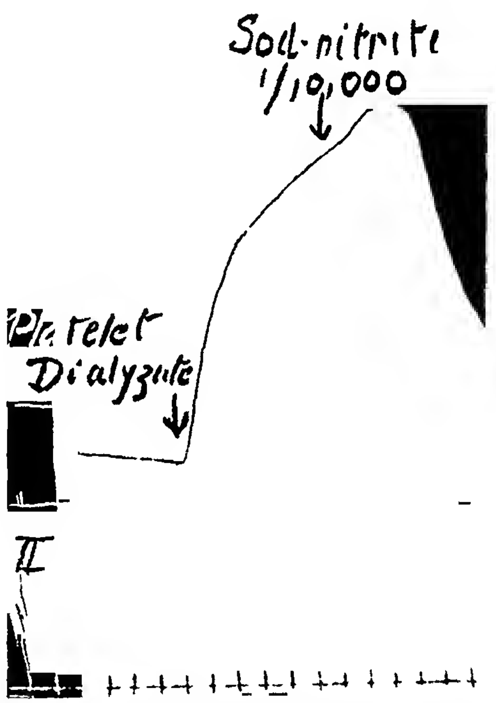

Fig 12—Experiment 40 Ox carotid Aqueous extract of pure platelets of ox restored to tonicity and dialyzed against an equal volume of Ringer-Locke solution Effect of dialyzate shown Time in half minutes

by repeated dialysis In this respect again defibrinated blood and platelet extract are similar The rapidity and completeness of the dialysis is further evidence against the identity of the vasoconstrictor substance with protein

Qualitative Tests—Several active solutions were tested for protein The dialyzate of defibrinated blood of Experiment 36 was tested by means of the heat-acid, biuret, potassium ferrocyanid and acetic acid, phosphotungstic acid and sulphuric acid tests An active extract of platelet substance by means of chloroform and another by means of alcohol were examined with the biuret test All these tests were

negative It is possible, therefore, to obtain active vasoconstrictor substance free from protein

Extraction in Relation to Protein—By the methods already described, five alcohol extracts, five ether extracts and six chloroform extracts of platelet substance were made All of the first, three of the second, and four of the third caused definite or marked vasoconstriction As protein is precipitated by all these fluids,[44] the extracts are protein-free, as was demonstrated in the two qualitative tests described The presence of vasoconstrictor substance in these extracts is therefore further evidence against its being a protein

Summary and Discussion—These results bring out several points in common between the vasoconstrictor substance of platelets and that of defibrinated blood Both constrict the coronary artery and both resist boiling for a short period Both dialyze very readily These results substantiate the conclusion already reached that both substances have the same origin, that is, the platelets The action on the coronary artery of both substances is diametrically opposed to that of epinephrin The vasoconstrictor substance of the platelets is not precipitated by heat and acid, dialyzes readily and completely, is present in vasoconstrictor material that is protein-free, and also in numerous active extracts obtained by means of fluids in which protein is insoluble—alcohol, chloroform and ether It is therefore neither epinephrin nor protein

Extraction—The method of preparing the extracts has already been described That of comparing different fluids with respect to the contents of vasoconstrictor substance follows

Method—Since different test objects varied in their sensitiveness, it was necessary to compare the different fluids on the same test object As most of the constrictions were very marked, and of a type which persisted for an indefinite period, even after washing with Ringer-Locke solution, some method of relaxing the arterial strip to its original tonus was necessary Sodium nitrite in a concentration of 1 10,000 in Ringer-Locke solution served this purpose A prompt fall, sometimes after a short further rise, resulted The preparation was then washed several times with Ringer-Locke solution, and after coming to its original level, was again used This stimulation of the preparation, first by constricting agents and then by dilating agents, did not impair the sensitiveness of the preparation The advantage of this method lies in the ability to use the same test objects for successive tests at relatively short intervals of not more than half an hour Two methods of comparing different substances were used The first consisted in comparing the vasoconstriction produced by them at the same dilution, a comparison which proved less accurate than the second method unless gross differences were present The other consisted in making parallel series of dilutions of the two substances Beginning with the highest dilution of the first substance, the dilutions were tested in order until a definite constriction of the arterial strip took

44 Hammarsten, O A Textbook of Physiological Chemistry, John Wiley & Sons, New York, 1909, p 61

place Each dilution was washed out with several changes of Locke's solution Thus what might be called the threshold concentration was determined This determination was repeated with the second substance That substance which caused a constriction at the greater dilution was judged the more vasoconstrictor of the two In order to prove that the sensitiveness of the preparation had not changed, the threshold concentration of the first substance was redetermined In comparing extracts with residues it was found, however, that dilution by weight and volume gave misleading results, since the extracts contained no salts, whereas the residue contained a relatively large bulk of them For these reasons comparisons were instituted on the basis of the volume of the blood from which the platelets were obtained Both extract and residue were made up to this volume, or else to some simple multiple or fraction of it This method furnished a basis for comparison which was uninfluenced by the amount of impurities in the fluids examined

TABLE 6—Absolute Alcohol Extraction of Platelet Substance

Exper	Constriction	Material	Method	Time	Temperature	Concentration
75	+++	Extract	Evap Dish	10 min	Room	1 1,000
	++	Residue	Evap Dish	10 min	Room	1 10
92	+++	Extract	Soxhlet	1½ hr	Warm	Vol = 10 c c
	Trace	Residue	Soxhlet	1½ hr	Warm	Vol = 10 c c
94	+	Extract	Soxhlet	3 hr	Warm	1 16*
	Trace	Residue	Soxhlet	3 hr	Warm	1 1*
114	+++	Extract	Soxhlet	4 hr	Warm	1 1*
	+	Residue	Soxhlet	4 hr	Warm	25 1*
161	++	Extract	Evap Dish	3½ hr	Room	Diluted 1 2
	++	Residue	Evap Dish	3½ hr	Room	Undiluted

* Concentration in terms of original blood volume

Alcohol Extraction—Five experiments were performed The results are shown in Table 6 In Experiment 75, extraction with absolute alcohol at room temperature for ten minutes yielded a product which caused a maximal constriction when diluted 1 1,000 with Ringer-Locke solution, whereas the residue caused a less marked constriction when diluted 1 10 In Experiment 92, extraction for one and one-half hours by means of the Soxhlet apparatus yielded a product which caused a maximal constriction when diluted with 10 c c of Ringer-Locke solution, whereas the residue, diluted to the same volume, caused only a trace of constriction In Experiment 94 similar extraction for three hours yielded an extract which caused a moderate constriction at a concentration of 1 16 The residue caused even less constriction at a concentration as high as 1 1, both concentrations being expressed in terms of original blood volume The same relation is apparent in Experiment 114, which will be described in detail

Method—Defibrinated blood was obtained from the ox Two liters of citrated blood were also obtained, and divided into two 1-liter portions From each liter the platelets were isolated by centrifuging in the usual manner The materials used in the experiment were obtained as follows

A Platelets from 1 liter of blood were ground up with plaster-of-Paris and distilled water and the mass was allowed to dry It was kept on ice and on

the following day extracted in the Soxhlet apparatus over a water bath, with 50 c c of absolute alcohol, for four hours The extract was then evaporated to dryness on the electric stove under a current of air, and was rather hot when removed The gummy substance on the dish was taken up with 100 c c of Ringer-Locke solution, filtered, and diluted for testing This was called A The plaster residue was taken up with 20 c c of water, and 20 c c of double strength Ringer-Locke solution added This was called A residue

B Platelets from the other liter of blood were kept on ice overnight, then rubbed in a mortar with 50 c c of water, then 50 c c of double strength Ringer-Locke solution added, and dilutions made for the tests This was called B

C Defibrinated blood was kept on ice over night and diluted for testing This was called C

All dilutions were made on the basis of original blood volume The concentrations are expressed as fractions or multiples of that concentration which resulted when the substance was made up to original blood volume For example, 1 20 means a concentration 1 20 of this standard, 25 1 means twenty-five time as concentrated, and 1 1 means the same concentration as the standard

Results—The results are shown in Figure 13 Defibrinated blood (C) caused a sharp constriction at 1 50 The alcohol residue (A residue) caused a relatively slight constriction at 25 1 The alcohol extract (A) tested in samples of increasing concentration, caused an extreme constriction at 1 1 The platelets (B) tested in a similar fashion, caused a definite constriction at 1 20 Defibrinated blood (C) again caused a sharp constriction at 1 50, showing that the arterial strip had not lost in sensitiveness Finally, the platelets (B) caused an extreme constriction at 1 10

The threshold concentrations of the four substances expressed in terms of original blood volume were

Defibrinated blood	(C)	1 50
Platelets	(B)	1 20
Alcohol extract	(A)	1 1
Alcohol residue	(A res)	25 1

From these figures it will be seen that the platelets were 2/5 as active as the defibrinated blood That is, 2/5 of the total potential vasoconstrictor power of blood was recovered in the platelets, in spite of the unavoidable loss occasioned by centrifuging The alcohol extract was 1/20 as active as the platelets, and the residue 1/25 as active as the extract

In Experiment 161 the residue produced about the same constriction as the extract in twice as great a concentration, a result less striking than those enumerated above

The extracts in all five experiments yielded much more vasoconstrictor substance than the residue This result was naturally most striking in the experiments in which, as in Experiment 114, the extraction was performed by means of the Soxhlet apparatus, but it was also true in the experiments in which it was performed by stirring at room temperature in an evaporating dish for a relatively short period

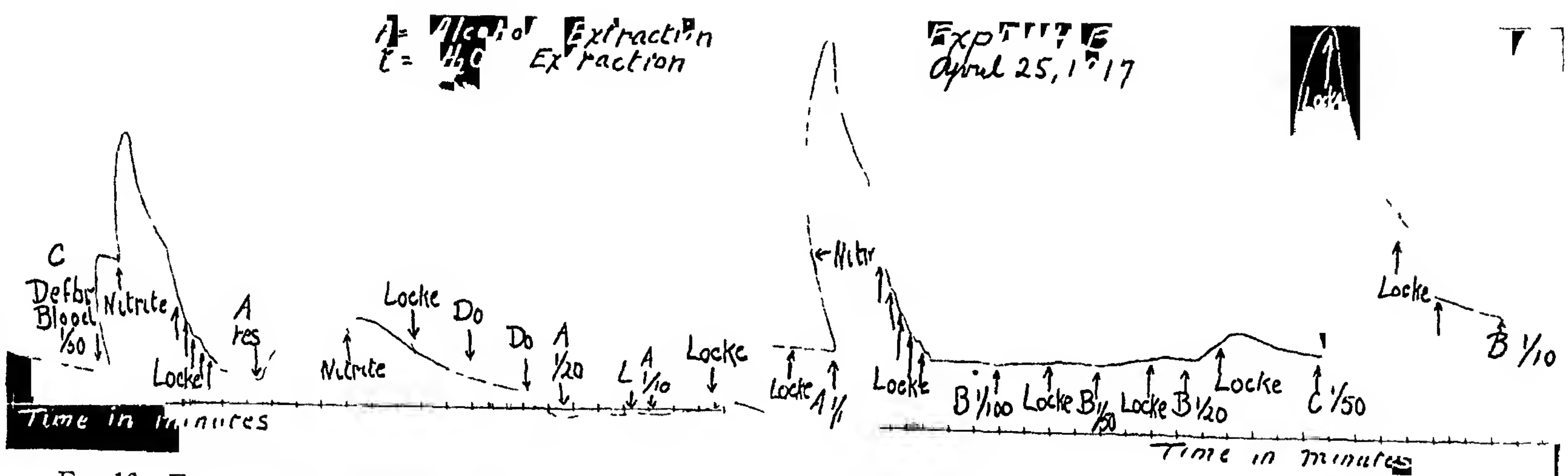

Fig 13—Experiment 114-114 B Ox carotid Abbreviations used (C) defibrinated blood, (Nitr) sodium nitrate 1 10,000, (A res) residue after alcohol extraction, (A) alcohol extract, (B) platelets plus water, plus double Ringer-Locke solution

Ether Extraction—The results of ethereal extraction are shown in Table 7 In Experiment 80, extraction at room temperature yielded a product which caused a moderate relaxation when diluted with Ringer solution 1 2,500 The dried platelet substance from which this extract was made caused a moderate constriction when diluted the same amount In Experiment 84 extraction for one hour in the Soxhlet apparatus failed to yield a product which, when diluted with 10 c c of Ringer-Locke solution, had any effect on the excised artery Only after overnight extraction was an active product obtained The like is true of Experiment 90, in which the extract by means of the Soxhlet apparatus for one hour caused only a trace of constriction Extract from the same material from the second to the twelfth hour inclusive caused a moderate constriction at a dilution about fifteen times as great In Experiment 92 the extraction was continued over-

TABLE 7—ETHER EXTRACTION OF PLATELET SUBSTANCE

Exper	Constriction	Material	Method	Time	Temperature	Concentration
80	Relaxation	Extract	Evap Dish	35 min	Room	1 2,500
	+	†				1 2,500
84*	0	Extract	Soxhlet	1 hr	Warm	10 c c Locke
	+++	Extract	Soxhlet	Overnight	Warm	10 c c Locke
90	Trace	Extract	Soxhlet	1 hr	Warm	1 870
	+	Extract	Soxhlet	2 12 hrs	Warm	1 120 000
92	+++	Extract	Soxhlet	Overnight	Warm	Vol = 10 c c
	++	Residue	Soxhlet	Overnight	Warm	Vol = 10 c c

* Platelets obtained from ⅔ liter of blood in each extraction
† Original Subs not extracted

night and the products diluted with 10 c c of Ringer-Locke solution The extract caused a maximal constriction, the residue a constriction that was almost maximal The results may be summarized by saying that extraction by ether for a period of an hour or less, whether in an evaporating dish or in the Soxhlet apparatus, yielded little or no vasoconstrictor substance, and that although overnight extraction yielded an extraction somewhat more active than the residue, the activity of the two was of the same order

Chloroform Extraction—The results are shown in Table 8 In Experiment 49, extraction of dried platelet substance for a few minutes at room temperature yielded a product which, when dried and diluted with 25 c c of Ringer-Locke solution, caused only a trace of constriction In Experiment 52, a similar process yielded an extract which caused a moderate constriction and a residue which caused a maximal constriction, both being diluted to the same extent In Experiment 78 the extract, when diluted with 6 c c of Ringer-Locke solution, caused only the same amount of constriction as the residue

when diluted with 250 c c In these experiments, short extraction at room temperature yielded an extract much less active than the residue In Experiment 92, extraction by means of the Soxhlet apparatus yielded a product which had no effect on the excised arterial strip when diluted to a volume of 10 c c, whereas the residue when diluted to the same volume, caused a maximal constriction As the overnight extraction in this experiment proceeded very slowly, it was continued for one and one-half hours over a boiling water bath In Experiment 94, extraction by the same apparatus over a water bath for three hours yielded an extract which caused the same constriction as the residue only when five times as concentrated These results may be summarized by saying that little or no active substance was extracted by chloroform in a period of ten minutes or less, and that the amount obtained by more prolonged extraction was considerably less than that remaining in the residue

TABLE 8—CHLOROFORM EXTRACTION OF PLATELET SUBSTANCE

Exper	Constriction	Material	Method	Time	Temperature	Concentration
49	Trace	Extract	Evap Dish	Minutes	Room	Undiluted
52	+	Extract	Evap Dish	Minutes	Room	Vol = 10 c c
	+++	Residue	Evap Dish	Minutes	Room	Vol = 10 c c
78	++	Extract	Evap Dish	10 minutes	Room	Vol = 6 c c
	++	Residue	Evap Dish	10 minutes	Room	Vol = 250 c c
92	0	Extract	Soxhlet	Overnight	Warm	Vol = 10 c c
	+++	Residue	Soxhlet	Overnight	Warm	Vol = 10 c c
94	0	Extract	Soxhlet	3 hours	Warm	1 2*
	++	Extract	Soxhlet	3 hours	Warm	5 1*
	++	Residue	Soxhlet	3 hours	Warm	1 1*

* Concentration in terms of original blood volume

Qualitative Tests for Cholesterol—In Experiment 94, referred to in Tables 6 and 8, two extracts were tested for cholesterol by means of the acetic anhydrid—sulphuric acid (H_2SO_4) test The first, a chloroform extract, contained a bare trace of cholesterol, estimated at 0 00001 gm, the second, an alcohol extract, although ten times as powerful, gave an even fainter reaction for cholesterol

Summary—The readiness with which the vasoconstrictor substance is extracted by means of alcohol, contrasted with the difficulty with which it is extracted by chloroform and ether, throws some light on its chemical nature It almost certainly excludes it from the group of cholesterol and allied substances This statement receives support from the qualitative tests for cholesterol The possibility that the alcohol in the Soxhlet experiments was warm enough to extract cholesterol, does not vitiate this conclusion, because even at room temperature a relatively short period of extraction with alcohol sufficed to dis-

solve the greater part of the vasoconstrictor substance That the results failed to show a sharp distinction between the action of the two types of extractives may be explained in one of two ways either more than one vasoconstrictor substance is present in the platelets, or the solubilities of a single substance are modified by the presence of a complex group of impurities

PART IV

RELATION OF THE VASOCONSTRICTOR SUBSTANCE TO THE FACTORS CONCERNED IN THE COAGULATION OF THE BLOOD

Although our study of this phase of the subject was partly incidental to other observations and cannot be regarded as complete, it seems worth recording It was considered from the point of view, first, of the time relation of the elaboration of the vasoconstrictor substance to the formation of the blood clot, second, of the effect of certain of the factors concerned in coagulation, and third, of the effect of heat on the vasoconstrictor substance as compared to the effect of certain of the factors concerned in coagulation In discussing these factors the terminology of Howell's theory[45] will be used

Method—To determine whether or not the elaboration of the vasoconstrictor substance preceded the formation of clot, a specimen of blood containing no anticoagulant was withdrawn from the carotid artery of the dog and brought into contact with an arterial strip within thirty seconds, and the effect noted Absence of coagulation was judged by the fact that the fluid could still be aspirated through a small glass tube In another experiment the effect of gross coagulation on the arterial strip immersed in an avian plasma was observed, the onset of coagulation being judged by the cessation of the bubbles of oxygen In three experiments the effect of citrated blood of the dog on the arterial strip was noted in connection with very careful examination for macroscopic clots Of the coagulation factors, thromboplastin was obtained by making tissue extracts Kephalin was prepared from the brain of the dog The larger vessels were dissected away, and the brain ground in a mortar with sand (Kahlbaum) in the presence of distilled water Double strength Ringer-Locke solution was then added in volume equal to that of the distilled water, and the mixture was filtered Extracts were made by means of Ringer-Locke solution of brain, spleen, and bone marrow, of the dog and of thymus and lymph nodes of the ox The thrombin was very kindly furnished by Dr Howell Prothrombin was obtained from plasma of the dog by Howell's method[46] The brain extract was tested for thromboplastic activity on one occasion and found to coagulate herudin plasma The thrombin was also tested and found to coagulate both herudin blood and plasma No systematic tests of the activity of the coagulation factors was undertaken In regard to the effect of temperature, the behavior of the platelet extract with respect to heat has been described in Part III, and that of the coagulation factors has been studied by other investigators

Results—That the elaboration of the vasoconstrictor substance precedes the formation of macroscopic clot is shown by an experiment

45 Howell, W H Am Jour Physiol, 1911, **29**, 187

in which a specimen of blood was withdrawn from the carotid artery of the dog without the use of anticoagulant, and placed in contact with the artery preparation within thirty seconds An abrupt powerful constriction resulted That coagulation was not yet complete was shown by the fact that after the writing point had risen 2 inches on the drum, removal of the blood by aspiration through a narrow tube was accomplished Again, an avian plasma, obtained by centrifuging blood of the hen in the cold, caused a great but gradual constriction which lasted for several minutes before the completion of coagulation was shown by the cessation of the flow of oxygen This event was without further influence on the curve Moreover, in three experiments in which citrated blood of the dog caused a definite, though moderate, constriction, subsequent examination of the blood by passing it through a fine sieve demonstrated that macroscopic clotting had not yet occurred These observations indicate that elaboration of vasoconstrictor substance precedes the development of the clot and are in accordance with those already cited by Kahn[26] and Stewart and Zucker [19]

As to the factors concerned in coagulation, a single experiment on prothrombin showed that it failed to influence the excised artery The same was true of a mixture of thrombin with brain extract Thromboplastin as obtained from brain, spleen, and thymus produced either no effect or else a slight relaxation, and extracts of lymph nodes alone had any vasoconstrictor effect The elaboration of vasoconstrictor substance, then, precedes the development of a macroscopic clot, and, on the other hand, the coagulation factors tested failed to cause vasoconstriction The resistance of the vasoconstrictor substance to heat has already been described

Discussion—Of the factors concerned in coagulation, fibrinogen, prothrombin and antithrombin are all present in the normal circulating blood, which, as our experiments almost certainly demonstrate, contains no vasoconstrictor substance Therefore, these factors have no vasoconstrictor effect in the proportions in which they occur in the circulating blood, and are thus unlikely to have any effect separately None of them is a crystalloid, whereas, we have shown the vasoconstrictor substance to be crystalloid Further, none of them is thermostable Fibrinogen is precipitated at 60 C (Howell[46]) Prothrombin extracts heated to 60 C undergo a marked diminution of their activity (Howell[49, 46]) Antithrombin is destroyed at 80 C [45] Of the factors evolved in shed blood, thrombin, though resistant in aqueous solutions, is destroyed by boiling for one minute in the presence of 1 per cent sodium chlorid (Howell[47]) Thromboplastin alone, of all

46 Howell, W H THE ARCHIVES INT MED, 1914, **13,** 76
47 Howell, W H Am Jour Physiol, 1914, **36,** 1

the factors concerned in coagulation, resists heat Thus Howell[48] obtained a splenic extract, the thromboplastic action of which was not affected by boiling The fact that blood platelets, as demonstrated by Bayne-Jones[37] and confirmed by Howell,[49] contain both prothrombin and thromboplastin, suggests the identity of the latter with the vasoconstrictor substance This suggestion receives support from the work of Lee and Vincent,[50] who observed that the thromboplastic activity of platelets was not destroyed in fifteen minutes at 120 C That the vasoconstrictor substance is identical with the thromboplastic substance of blood platelets is therefore possible The fact, however, that thromboplastin is present in all the tissue extracts mentioned, whereas the vasoconstrictor substance is found only in extracts of lymph nodes and of platelets, renders that possibility remote Solely from the behavior of the respective substances toward heat, the nonidentity of vasoconstrictor substance with any of the clotting factors may be inferred, and this conclusion is strengthened by our other observations already mentioned It may be concluded that the vasoconstrictor substance has no probable relation either to the actual formation of the blood clot or to the factors concerned in coagulation

CONCLUSIONS

1 Uncoagulated blood of the ox or calf has no constrictor action on the excised strip of the ox carotid

2 Blood platelets of ox, dog or pig yield an extract which has a powerful vasoconstrictor action

3 Erythrocytes yield no vasoconstrictor substance

4 Leukocytes, as represented by the cells of the pleural exudate of the dog, yield none

5 Plasma can be obtained free of vasoconstrictor substance Its constrictor action, when present, is probably due to changes occurring after it leaves the blood vessels The circulating plasma of normal animals has probably no such vasoconstrictor action

6 The vasoconstrictor substance (or substances) is neither protein nor epinephrin It is a crystalloid more readily extracted by water or alcohol than by ether or chloroform, and is probably not related to cholesterol

7 The vasoconstrictor substance, though present in coagulated blood, is not dependent on the actual formation of the blood clot, nor is it related to any of the factors concerned in coagulation, with the possible exception of thromboplastin

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48 Howell, W H Am Jour Physiol, 1912, **31,** 1

49 Howell, W H Am Jour Physiol, 1914, **35,** 474

50 Lee, R I, and Vincent, B The Archives Int Med, 1914, **13,** 398

RELATION BETWEEN THE PLATELET COUNT OF HUMAN BLOOD AND ITS VASOCONSTRICTOR ACTION AFTER CLOTTING*

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The effect of defibrinated blood and of blood serum in producing contraction of arterial smooth muscle, either in a perfused organ or in a surviving artery suspended in a chamber, has long been observed It was the cause for many erroneous reports of the finding of epinephrin in the circulating blood until the work of O'Connor[1] showed clearly that the vasoconstrictor property is not due to epinephrin, but is developed in connection with the process of coagulation and is not possessed by blood kept fluid by anticoagulants O'Connor's conclusions were confirmed and extended by Stewart,[2] Schultz,[3] Stewart and Harvey,[4] and Janeway and Park[5] While this demonstration is of importance clinically, chiefly because it discredits all previous work on the supposed detection of epinephrin in shed blood, and invalidates all conclusions therefrom as to the cause of arterial hypertension, nevertheless the problem of the origin and nature of the vasoconstrictor property of shed blood has an independent interest Its solution may not only facilitate studies on the properties of blood in hypertensive patients, but may have practical importance in connection with the purpuric diseases and the disturbances of the highly complex changes concerned in the coagulation of the blood

The studies of Janeway, Richardson and Park,[6] reported in this journal, make certain that this vasoconstrictor property is developed chiefly, if not solely, in connection with the disintegration of the blood platelets The importance of the platelets as a source of the vasoconstrictor substance had already been recognized by Zucker and Stewart[7] and by Le Sourd and Pagniez,[8] but without convincing dem-

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1 O'Connor, J M Munchen med Wchnschr, 1911, **58,** 1439, Ibid, Arch f exper Path u Pharm, 1912, **67,** 195
2 Stewart, G N Jour Exper Med, 1911, **14,** 377
3 Schultz, W H Bull Hygienic Lab, U S Public Health Service, 1912
4 Stewart, H A, and Harvey, S C Jour Exper Med, 1912, **16,** 103
5 Janeway, T C, and Park, E A Jour Exper Med, 1912, **16,** 541
6 Janeway, T C, Richardson, H B, and Park, E A This issue, p 565
7 Zucker, T F, and Stewart, G N Zentralbl f Physiol, 1913, **27,** 85
8 Le Sourd, L, and Pagniez, Ph Compt rend Soc de biol, 1914, **1,** 587

onstration In connection with the work reported by Janeway, Richardson and Park,[6] the experiments which follow were carried on in an endeavor to add a further link to the chain of evidence connecting the blood platelets with the development of vasoconstrictor properties by shed blood

The experiments consisted in the comparison of the degree of vasoconstriction produced in the same ox artery by two specimens of defibrinated human blood of known platelet content The strength of vasoconstrictor action was estimated in two ways (1) By the form and height of the curve written on the drum by the lever connected with the artery, (2) by determining the extinction point of the vasoconstrictor action in successive dilutions of the blood, that is, the threshold concentration of vasoconstriction Details of the various methods employed follow

So far as I have been able to discover, this is the first systematic comparison of platelet count with vasoconstrictor effect It is true that Sakai and Hiramatsu[9] compared the blood serum of patients suffering from beriberi with that of normal persons, using as a standard the effect of a known concentration of epinephrin In this disease they found the blood platelets to average three times the normal They undertook, however, no systematic count of the blood platelets of those patients whose serum they examined With reference to the subject of this paper, their work may be regarded as suggestive rather than conclusive

METHODS

Of the methods employed for the clinical estimation of the number of blood platelets in the circulation, that of Wright and Kinnicutt[10] seemed the most practicable The principle of this method is the use of special staining solutions in conjunction with the ordinary apparatus used in estimating the red corpuscles of the blood These solutions are two in number (1) potassium cyanid in 1 400 solution, and (2) cresyl blue in 1 300 solution These were kept separately on ice and mixed in the proportion of 3 2 immediately before counting The mixture was filtered A drop of blood was taken from the ear of the patient by means of a needle and drawn into a 1 100 diluting pipet, such as is used in the ordinary estimation of red corpuscles The special solution was then drawn up to the 101 mark and the counting was carried out as for red corpuscles The effect of this solution was to remove the ordinary cells and leave stained platelets The Thoma-Zeiss apparatus was used as a counting chamber As the special thin cover glasses recommended by Wright and Kinnicutt for counting of platelets were not available, those furnished by Zeiss were used In counting, certain precautions were observed The cells were counted as soon after mixing as possible Dust was carefully avoided, as its particles are often the same size as the platelets, although usually distinguishable by their dark staining and irregular outlines Results were checked in every case by a second count The estimations were made on the day of the experiment

The test object used in these experiments is a modification of Meyer's excised

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9 Sakai, S, and Hiramatsu, T Mitt a d med Fak d kais Univ zu Tokyo, 1914, **13**, 177

10 Wright, J H, and Kinnicutt, R Jour Am Med Assn, 1911, **56**, 1457

strip of the ox carotid It has been described in detail in the paper by Janeway, Richardson and Park[6] A brief description is sufficient here From the carotid artery of the ox a ring was cut This ring was cut open, ligatured at each end, and suspended in Locke's solution in such a way that the tension was exerted on the circular muscle fibers The upper end of this strip was attached to the short arm of a lever, the long end of which wrote on a drum with a magnification of 15½ Through the solution a constant stream of oxygen was kept bubbling Artery and solution were contained in a small test tube which was suspended in a large water bath maintained at 38 C by means of an electric thermostat Through a tube fused to the bottom of the test tube the fluid could be aspirated, and then replaced from above by means of an ordinary pipet This arrangement permitted complete exchange of fluid with a minimum of mechanical disturbance The arteries were collected in ice-cold Locke's solution and kept on ice until needed The excised strip was stretched with a weight of 90 gm for twenty minutes, at the end of which the weight was reduced to a load of 30 gm for the experiment It was then allowed to come to equilibrium

Twenty c c of blood were withdrawn from the vein of the patient's arm by means of a needle and syringe The blood was defibrinated immediately by beating it with a rubber brush in an evaporating dish In each experiment comparison was made between the blood of two patients with reference to their platelet count, a blood of high platelet count with one of low platelet count Since different test objects varied in their sensitiveness, it was necessary to compare the different specimens on the same test object The obvious method of so doing, that is, comparison of the degree of constriction produced by the two specimens, having proved unreliable, another method was adopted Parallel series of dilutions were made of the two specimens Beginning with the highest dilution of the first specimen, the dilutions were tested in order until a definite reaction on the part of the arterial strip took place Each specimen was washed out by three changes of Locke's solution Thus, what might be called the threshold concentration was determined This determination was repeated with the second specimen That specimen which caused a constriction at the higher dilution was judged the more vasoconstrictor of the two In order to make sure that the sensitiveness of the preparation had not changed, the threshold concentration of the first specimen was redetermined By this means a comparison of vasoconstrictor effect was attained which was far more accurate than any attempt to judge the degree of constriction produced by the undiluted blood

RESULTS

Fourteen experiments were performed, in which blood from twenty-eight patients was examined The results are indicated in Table 1 Perhaps the meaning of the table will be best illustrated by an example, say Experiment 8 In this, blood from a patient whose platelets numbered 205,000 caused a definite constriction in a dilution of 1 8 Blood from another patient whose platelets numbered 248,000 caused a constriction in the same dilution Therefore, both samples had about the same vasoconstrictor effect Again, in Experiment 6, blood from a patient whose platelets numbered 51,000, diluted with an equal volume of Locke's solution, gave no constriction, whereas blood from a patient whose platelets numbered 491,000 gave a very marked constriction when diluted with two volumes of Locke's solution In this case the second sample had much the greater constrictor effect If, then, this table is examined with reference to the degree of

TABLE 1.—Data of Experiments

Experiment No.	Date	Source of Blood		Platelet Count	Dilution	Degree of Constriction
		Med. No.	Diagnosis			
I	5/23/17	38142	Pernicious anemia	85,000	1:25 1:10	∓ +
		37838	Syphilis (W.), aneurism of arch of aorta	262,000	1:25	+
II	6/ 4/17	38070	Syphilis (W.), syphilis of aorta, dilated aortic arch, aortic insufficiency, myocardial insufficiency	270,000	1:10 1:5	∓ +
		37880	Carcinoma of stomach, tuberculosis of pleura	867,000	1:10	+
III	6/11/17	37961	Cirrhosis of liver	95,000	1:5 1:1	— —
		38000	Chronic nephritis (?), hypertension	235,000	1:25	+
IV	6/25/17	38113	Chronic myeloid leukemia	332,000	1:2	∓
		38028	Chronic myeloid leukemia	868,000	1:4	+
V	7/ 9/17	38136	Syphilis (W.), secondary anemia	63,000	1:1	—
		38215	Chronic infectious arthritis, pyorrhea alveolaris, intestinal parasitism (Ascaris lumbricoides)	218,000	1:2	+++
VI	7/23/17	38551	Pernicious anemia	51,000	1:1	—
		38285	Pulmonary tuberculosis, pyorrhea alveolaris, visceroptosis	491,000	1:2	+++
VII	9/14/17	Genl. No. 119451	Myeloid leukemia	48,000	1:1	+
		38479	Pellagra ?	283,000	1:2	+++
VIII	9/19/17	Genl. No. 120097	Pernicious anemia	205,000	1:8	+
		38484	Arteriosclerosis, hypertension, myocardial insufficiency, chronic nephritis	248,000	1:8	+
IX	10/ 9/17	Genl. No. 119451	Myeloid leukemia	33,000	1:1	—
		Genl. No. 120268	Chronic nephritis	246,000	1:2	+++
X	10/12/17	Genl. No. 120652	Pernicious anemia	81,000	1:4 1:2	— +
		38628	Polycythemia, cerebral thrombosis, hemiplegia (right), aphasia	346,000	1:2	++

TABLE 1—Data of Experiments—(*Continued*)

Experiment No	Date	Source of Blood: Med No	Source of Blood: Diagnosis	Platelet Count	Dilution	Degree of Constriction
XI	10/17/17	Genl No 120680	Chronic nephritis, secondary anemia	189,000	1 8 1 4	— +
		38628	Polycythemia	314,000	1 1	+
XII	10/30/17	Genl No 38636	Pernicious anemia	47,000	1 1	—
		120781	Acute nephritis with purpura	180,000	1 2	+++
XIII	11/ 2/17	Genl No 120597	Pernicious anemia	142,000	1 8	+
		Genl No 121133	Banti s disease	439,000	1 8	+
XIV	11/ 6/17	Genl No 121183	Cirrhosis of liver	39,000	1 2	+
		Genl No 121133	Banti's disease	302,000	1 2	+

Degree of constriction indicated by plus and minus signs — = no constriction, ∓ = constriction of one preparation and not of another, + = definite constriction, ++ = moderate constriction, +++ = marked constriction

Under dilutions the figures indicate the number of volumes of blood in relation to the number of volumes of Locke's solution used in diluting Thus, 1 1 means 1 volume diluted with 1 volume of Locke's solution

constriction as compared to the amount of dilution, it will be seen that blood from patients of a higher platelet count caused constriction at a higher dilution than blood taken from patients of a low platelet count, that is, in the former case, the threshold concentration is less In Experiment 11 only was the lower platelet count associated with the greater constriction In this experiment the difference in platelet count was relatively slight, 189,000 as compared to 314,000 In Experiments 13 and 14, bloods of different platelet count caused the same constriction Out of fourteen experiments, then, eleven show a direct proportion between platelet count and constrictor effect, one experiment only shows the reverse, and two experiments are equivocal

Examples of the curves obtained are shown in Figures 1 to 4 In Figure 1, blood from two patients was compared, the first having an abnormally high platelet count (868,000), the second a normal count (332,000) Neither blood caused a definite constriction when diluted with eight parts of Locke's solution, as seen on the curves at "II1/8" and "I1/8" These figures indicate that one volume of blood was diluted with eight volumes of Locke's solution The blood of high platelet count, Blood II, caused a definite constriction at a dilution of 1 4, Blood I, of lower platelet count, not until a dilution of 1 2 was reached Also the greater constriction caused by the former blood at each dilution is evident at a glance This figure exemplifies the greater vasoconstrictor effect associated with a platelet count above

normal In Figure 2, Experiment 5, blood of an abnormally low platelet count (63,000) is compared with blood of a normal platelet count The former had no effect when diluted with an equal volume of Locke's solution as shown under "I1/1," whereas the latter caused a very marked constriction in a dilution of 1 2, as shown under "II1/2" A second test of the first blood was again without effect This figure illustrates the lesser vasoconstrictor activity of a blood of lower platelet count In Figure 3 the platelets show a similar relation, and the curves almost exactly duplicate those of the preceding figure In

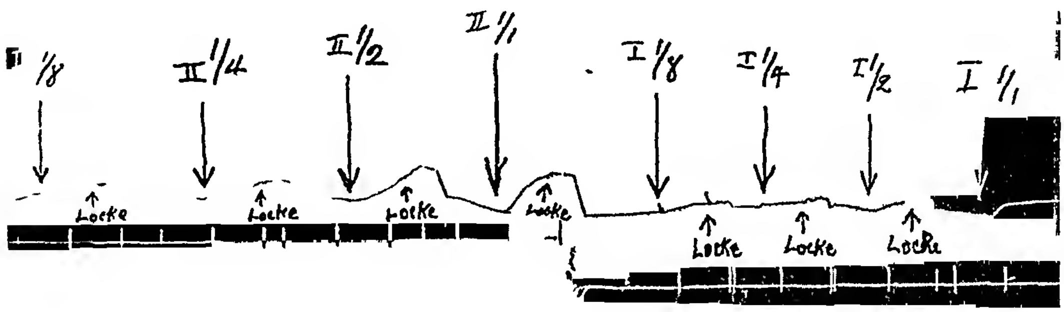

Fig 1—Experiment IV Effect of defibrinated blood in increasing concentration The fractions indicate the degree to which the blood was diluted Blood II Defibrinated blood from a patient whose platelets numbered 868,000 per c mm Blood I Defibrinated blood from a patient whose platelets numbered 332,000 per c mm Time minutes

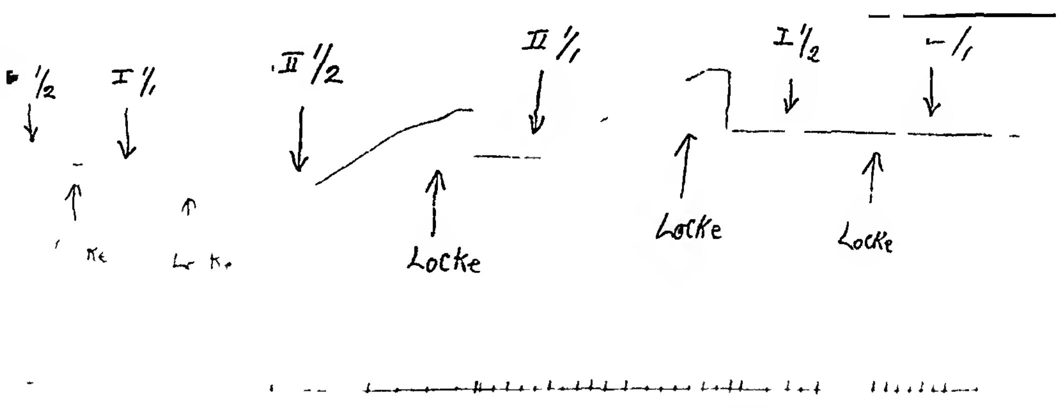

Fig 2—Experiment V Blood I Blood platelets, 63,000 Blood II Blood platelets, 218,000 Time minutes and half minutes (clock out of order)

Figure 4 it is demonstrated that bloods of approximately the same platelet count yield curves almost exactly parallel In fact, the curves produced by Blood II might be fairly accurately superimposed on those of Blood I The same parallelism was observed with each of two different artery preparations The figure further exemplifies the fact that the relation between the effects of two samples of blood remained the same with a second test-object as with the first

Although, as already stated, different test objects vary to such an

extent that no exact normal standard for the threshold concentration is possible, nevertheless a certain rough normal standard can be observed Blood taken from patients whose platelets numbered less than 100,000 was distinctly below this standard Nine such specimens were examined Of these, five caused no constriction when diluted

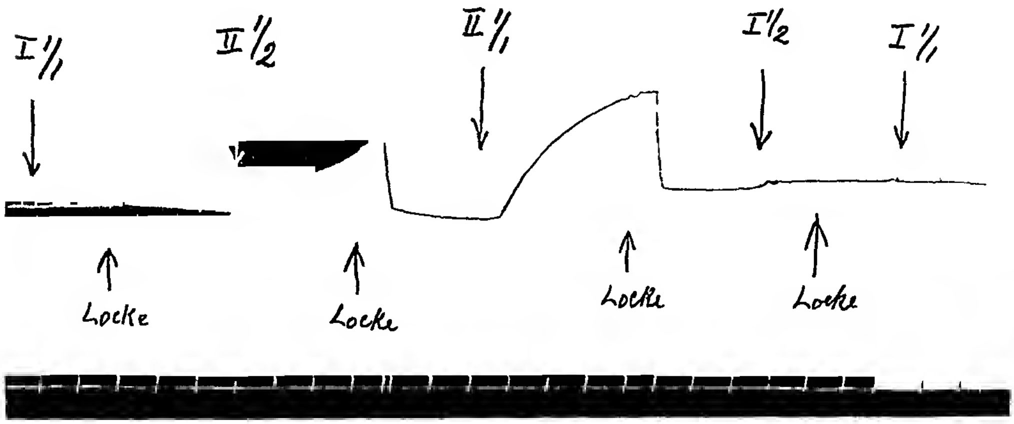

Fig 3—Experiment VI Blood I Blood platelets, 51,000 Blood II Blood platelets, 491,000 Time minutes

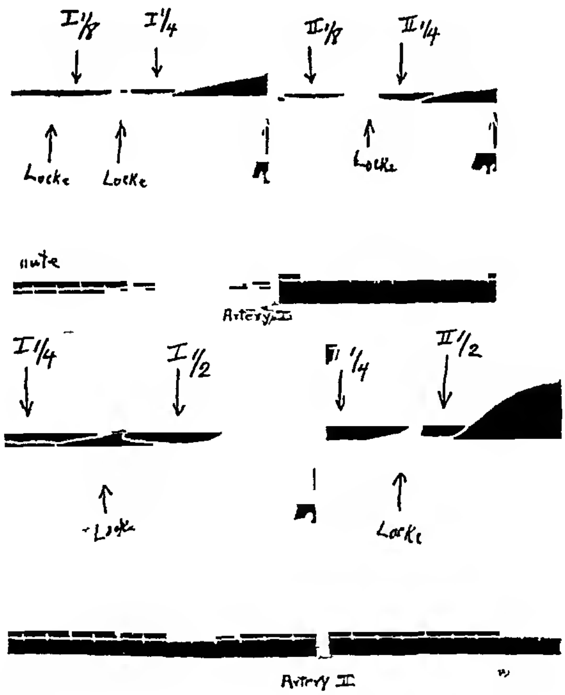

Fig 4—Experiment VIII Showing the effect of the same materials on two different preparations, Artery I and Artery II Blood I Blood platelets, 205,000 Blood II Blood platelets, 248,000 Time minutes

with an equal volume of Locke's solution The platelet counts in these five experiments were 95,000, 63,000, 51,000, 33,000, and 47,000 In Table 2 are shown the platelet counts of those cases which

TABLE 2—COMPARISON OF PLATELET COUNTS

Experiment No	Blood Giving No Constriction		Blood Giving Constriction	
	Diagnosis	Platelet Count	Diagnosis	Platelet Count
I			Pernicious anemia	85,000
			Syphilis (W), aneurysm of arch of aorta	262,000
II			Syphilis (W), syphilis of aorta, dilated aortic arch, aortic insufficiency, myocardial insufficiency	270,000
			Carcinoma of stomach, tuberculosis of pleura	867,000
III	Cirrhosis of liver	95,000	Chronic nephritis (?), hypertension	235,000
IV			Chronic myeloid leukemia	332,000
			Chronic myeloid leukemia	868,000
V	Syphilis (W), secondary anemia	63,000	Chronic infectious arthritis (spine), pyorrhea alveolaris, intestinal parasitism (Ascaris lumbricoides)	218,000
VI	Pernicious anemia	51,000	Pulmonary tuberculosis, pyorrhea alveolaris, visceroptosis	491,000
VII			Myeloid leukemia	48,000
			Pellagra (?)	283,000
VIII			Pernicious anemia	205,000
			Arteriosclerosis, hypertension, chronic nephritis, myocardial insufficiency	248,000
IX	Myeloid leukemia	33,000	Chronic nephritis	246,000
X			Pernicious anemia	81,000
			Polycythemia, cerebral thrombosis, hemiplegia (right), aphasia	346,000
XI			Chronic nephritis, secondary anemia	189 000
			Polycythemia	314,000
XII	Pernicious anemia	47,000	Acute nephritis with purpura	180,000
XIII			Pernicious anemia	142,000
			Banti's disease	439,000
XIV			Cirrhosis of liver	39,000
			Banti's disease	302,000

caused no constriction in the dilution indicated, as compared to those that did Only three specimens produced any constriction of the artery when diluted with two volumes of Locke's solution, and only four when diluted with equal volumes Two of these were from cases of pernicious anemia, one from a case of cirrhosis of the liver and the fourth from a case of myeloid leukemia Reference to Table 1 will show that, in general, specimens of bloods of a high platelet count caused constriction to a much greater degree or at a much higher dilution

No relation could be detected between the type of disease and the degree of vasoconstriction produced by the defibrinated blood In other experiments blood which had the property of digesting its own clot was tested after the autolysis No constriction resulted

SUMMARY

Fourteen experiments with twenty-eight different samples of defibrinated human blood of known platelet count have been described These experiments were performed by bringing the defibrinated blood into contact with the surviving carotid of the ox suspended according to Meyer's method and registering its degree of constriction on a revolving drum by means of a magnifying lever

In these experiments bloods of about equal platelet counts produced approximately the same degree of vasoconstriction With one exception, bloods of higher platelet count produced more marked constriction than bloods of much lower platelet count This one exception was the blood from a case of polycythemia with a count of 314,000, compared with blood from a case of chronic nephritis with a count of 189,000 The difference in platelet content here is relatively slight

Of nine specimens of blood with a platelet count less than 100,000, only three produced any constriction of the artery when diluted with two volumes of Locke's solution, and only four when diluted with equal parts of Locke's solution Two of these were from cases of pernicious anemia, one from a case of cirrhosis of the liver, and the fourth from a case of myeloid leukemia

CONCLUSIONS

1 The vasoconstrictor effect of defibrinated human blood on the surviving carotid of the ox is roughly proportional to the platelet count of the circulating blood

2 Bloods with platelet counts far below the normal develop little or no vasoconstrictor property when defibrinated

3 These findings emphasize the relation of the blood-platelets to the vasoconstrictor property developed in shed blood

CLINICAL CALORIMETRY

TWENTY-SIXTH PAPER

THE EFFECT OF A SMALL BREAKFAST ON HEAT PRODUCTION *

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AND

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NEW YORK

NOTE—It has been the custom of the Russell Sage Institute of Pathology to publish each year a group of seven or eight papers embodying the work of the previous season This year practically the whole staff is on active duty in the army or the navy and it has been considered advisable to present three of the papers without waiting for the whole series

It is hoped at a later date to publish the work on temperature regulation after the intravenous injection of typhoid vaccine, on metabolism in tubercular fever, in erysipelas, in acute and chronic arthritis, and also a summary of the diets that have been used in the metabolism ward It has been impossible this year to review the literature as fully as has been done in the other papers of this series

In order to compare the metabolism of different individuals, it has been customary to determine in each case the basal heat production This means that the subject must be studied in the morning hours, at complete rest, twelve to sixteen hours after the last meal Hundreds of patients and normal controls have been examined under these standard conditions, which are recognized in almost all the laboratories interested in the gaseous exchanges Obviously, it would be a mistake to try to alter the standard conditions in any manner that would change the results and render them unfit for comparison with the mass of material already accumulated at the cost of great labor All who have experimented with large numbers of subjects, however, have been obliged to listen to complaints from those who object to going without breakfast As a rule, this is not a serious matter, but it is best to have as few complaints as possible from the person who is to be the subject of an experiment which can be profoundly affected by ill humor or nervousness

Most observers have been afraid to allow their subject any breakfast, because they have believed that the specific dynamic action of the food would increase the metabolism above the basal level In the

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* From the Russell Sage Institute of Pathology, in Affiliation with the Second Medical Division of Bellevue Hospital

TABLE 1—DATA OF—

Subject Date, Weight, Surface Area, Ht Wt Formula	Period	End of Period, Time	Carbon Dioxid, Gm	Oxygen, Gm	R Q	Water, Gm	Urine N per Hour, Gm	Indirect Calorimetry, Cal	Heat Eliminated, Cal
J C F	Prelim	11 02							
11/10/16 62 7 Kg 1 80 Sq M	1	12 02	20 6	19 5	0 77	25 4	0 52	63 9	70 4
	2	1 02	22 4	19 6	0 83	24 7	0 52	65 4	69 0
	3	2 07	23 5	19 6	0 87	25 3	0 52	66 1	74 7
J C F	Prelim	11 06							
11/13/16 62 8 Kg 1 80 Sq M	1	12 06	22 4	19 1	0 85	29 0	0 34	64 3	77 0
	2	1 06	26 6	23 2	0 83	28 3	0 34	78 0	80 3
	Aver								
W H O	Prelim	11 19							
4/7/17 66 5 Kg 1 77 Sq M	1	12 19	21 7	19 8	0 80	29 3	0 39	65 9	69 6
	2	1 19	21 8	19 0	0 84	26 2	0 39	63 6	67 8
	3	2 19	21 4	20 1	0 77	27 4	0 39	66 5	67 9
	Aver								
W H O	Prelim	12 07							
4/9/17 66 6 Kg 1 77 Sq M	1	1 07	22 3	19 5	0 83	29 1	0 38	65 4	65 6
	2	2 07	21 8	21 2	0 75	28 7	0 38	69 2	67 6
D P B	Prelim	11 45							
11/21/16 65 2 Kg 1 81 Sq M	1	12 45	23 6	21 6	0 80	27 4	0 55	71 3	74 8
	2	1 45	24 6	22 7	0 79	29 9	0 55	75 2	75 1
	3	2 45	23 6	21 9	0 79	29 3	0 55	72 1	76 4
	Aver								
D P B	Prelim	11 45							
11/22/16 65 1 Kg 1 81 Sq M	1	12 45	24 3	21 4	0 82	29 4	0 58	71 4	73 9
	2	1 45	24 0	22 7	0 77	30 9	0 58	74 4	75 6
	Aver								
D P B	Prelim	12 15							
11/24/16 65 3 Kg 1 82 Sq M	1	1 15	26 1	23 1	0 82	32 6	0 57	76 8	74 7
	2	2 15	24 9	22 0	0 83	32 8	0 57	73 1	73 3
	3	3 15	24 3	22 5	0 79	32 3	0 57	74 2	73 6
E F D B	Prelim	11 46							
12/18/16 73 9 Kg 1 90 Sq M	1	12 46	25 0	23 3	0 78	38 0	0 44		79 2
	2	1 46	23 6	Leak		37 0	0 44		79 4
	3	2 46	23 6	23 0	0 75	37 0	0 44		78 5
	Aver 1 and 2							76 2	

—Calorimeter Experiments

Direct Calorimetry (Rectal Temp), Cal	Rectal Temp , C	Average Pulse	Work Adder, Cm	Non protein R Q	Per Cent Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd	Per Kg	Per Sq M (Ht -Wt)	
	36 3									Standard breakfast, 5 53 a m , asleep 20 min
68 6	36 3		10	0 76	22	64	14	1 02	35 5	Very quiet
65 0	36 2	56	7	0 84	21	42	37	1 04	36 3	Very quiet
76 8	36 3			0 89	23	28	49	0 97	33 9	Very quiet
	36 7	60								Basal
61 5	36 4		15	0 86				1 02	35 7	Fairly quiet
80 3	36 4	68	24	0 84				1 24	43 3	Restless, excluded from basal average
					13	45	42			
	36 5									Standard breakfast, 6 35 a m
69 3	36 5			0 80	16	59	25	0 99		Fairly quiet, slept 35 min
72 4	36 6			0 84	16	45	38	0 96		Quiet
67 5	36 6			0 77	15	66	19	1 00		Very quiet
									36 1	
	36 5									Basal
64 8	36 5		10	0 84	15	46	39	0 98	37 0	Very quiet
64 0	36 4		9	0 74	15	52	33	1 04	39 1	Very quiet
	36 8	70								Standard breakfast, 6 45 a m
54 5	36 5		5	0 80	20	55	25	1 09		Very quiet
75 3	36 5	64	6	0 78	19	60	21	1 15		Very quiet
82 6	36 6	64	7	0 78	20	59	21	1 10		Very quiet
									40 2	
	36 9									Basal
67 1	36 7	69	6	0 83	21	46	33	1 10		Very quiet
75 8	36 7	64	13	0 75	21	65	14	1 14		Very quiet
									40 0	
	36 7	75								Standard breakfast, 11 56 a m 12 01 p m
59 7	36 5	70	8	0 83	20	47	33	1 18	42 4	Asleep 15 min , very quiet
87 0	36 7		13	0 83	20	47	33	1 12	40 4	Very quiet
71 1	36 7	67	11	0 78	20	59	21	1 14	42 0	Very quiet
	37 0									Basal
75 7	36 9	60	13							Very quiet
71 6	36 8		12							Leak in oxygen, hour lost
81 1	36 8	60	15							
				0 76	15	71	14	1 03	40 1	

TABLE 1—Data of Calorimeter—

Subject Date, Weight, Surface Area, Ht Wt Formula	Period	End of Period, Time	Carbon Dioxid, Gm	Oxygen, Gm	R Q	Water, Gm	Urine N per Hour, Gm	Indirect Calorimetry, Cal	Heat Eliminated, Cal
E F D B	Prelim	11 37							
12/20/16 74 8 Kg 1 90 Sq M	1	12 37	26 9	24 0	0 82	39 1	0 47		81 0
	2	1 37	26 3	22 5	0 85	37 9	0 47		79 9
	3	2 37	24 6	23 6	0 76	38 1	0 47		79 5
	Aver							77 8	
L O'R	Prelim	11 56							
4/17/17 45 8 Kg 1 42 Sq M	1	12 56	17 2	15 3	0 82	29 2	0 31		57 1
	2	1 56	17 9	16 2	0 80	25 3	0 31		53 7
	Aver		17 5	15 8	0 81	27 2		52 5	55 4
	3	2 20							
	4	3 20	20 2	17 3	0 85	27 4	0 31	58 3	55 2
	5	4 20	19 5	16 4	0 87	25 9	0 31	55 4	54 3
	Aver		19 9	16 9	0 86	26 7	0 31	56 9	54 8

present paper it is possible to show that the increase caused by a small standard breakfast is so transient that it can safely be ignored two hours after the meal is taken As a result of the experiments here reported the custom has recently been adopted of allowing almost all the patients and normal controls to eat a small breakfast five or six hours before the observation begins In consequence of this change the subjects have been noticeably better humored and stand quite easily observations lasting until late in the afternoon Previous to the use of the small breakfast it was often necessary to end the calorimeter experiments about 2 o'clock in the afternoon, because the patients felt weak from lack of food

The subject of the specific dynamic action of food has been discussed in Papers 4, 7 and 21 of this series,[1] and it is fully reviewed by Graham Lusk[2] The increase in heat production following a large protein meal may amount to 46 per cent in man, and in the dog some

1 Gephart, Frank C, and Du Bois, Eugene F Clinical Calorimetry, Paper 4, The Determination of the Basal Metabolism of Normal Men and the Effect of Food, The Archives Int Med, 1915, **15,** 835 Coleman, Warren and Du Bois, E F Clinical Calorimetry, Paper 7, Calorimetric Observations on the Metabolism of Typhoid Patients With and Without Food, *Ibid*, 1915, **15,** 887 Aub, J C, and Du Bois, E F Clinical Calorimetry, Paper 21, The Basal Metabolism of Dwarfs and Legless Men with Observations on the Specific Dynamic Action of Protein, *Ibid*, 1917, **17,** 840

2 Lusk, Graham The Elements of the Science of Nutrition, Ed 3, Philadelphia, 1917

—Experiments—(*Continued*)

Direct Calorimetry (Rectal Temp), Cal	Rectal Temp , C	Average Pulse	Work-Adder, Cm	Non-protein R Q	Per Cent Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd	Per Kg	Per Sq M (Ht -Wt)	
	36 9									Standard breakfast, 11 18–11 23 a m
76 9	36 9	58	10							Very quiet
80 1	36 9	58	10							Very quiet
75 5	36 8	58	12							Very quiet
				0 81	16	55	29	1 05	41 0	
	37 0									Basal
54 5	37 0		7							Very quiet
51 9	36 9	85	7					1 15	37 0	Very quiet
53 2	36 9			0 81	16	55	29			
	37 0									Standard breakfast, 1 58–2 06 p m
52 9	37 0		6	0 85	14	43	43	1 27	41 1	Very quiet
53 6	37 0	91	1	0 88	15	35	50	1 21	39 0	Very quiet
53 8	37 0			0 87	15	39	46		40 1	

effect has been apparent for as long as twenty hours With carbohydrate and fat the effect is less striking, but a rise of 20 per cent is not uncommon Most experimenters have confined their attention to the results after large meals In order to study small meals the technic is difficult, since it is necessary to detect changes of 2 per cent in the heat production

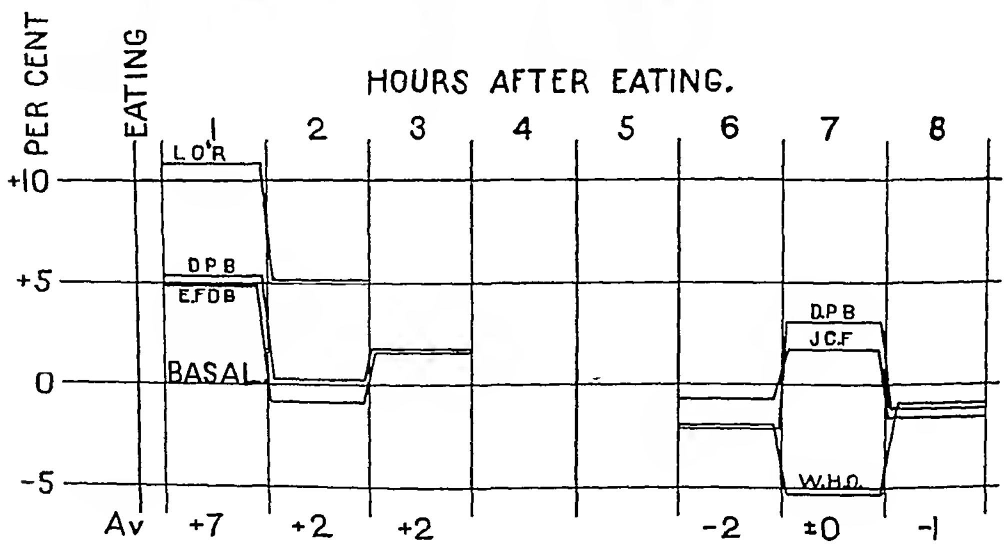
For this reason the subjects for the following experiments were chosen with great care All of them were laboratory workers thoroughly familiar with the calorimeter, and they appreciated the importance of remaining quiet Four of the subjects were men, one was a woman Although their weights varied between 45 and 74 kg, they were all given exactly the same amount of food The standard breakfast selected consisted of a slice of bread (30 gm) with 8 gm. butter and a cup (200 c c) of caffein-free coffee (Kaffee Hag) containing 10 gm cane sugar and 60 c c milk This contains 4 7 gm protein, 9 0 gm fat and 28 9 gm carbohydrate, a total of 222 calories, using the following figures as the average composition of the foods taken

	Protein, Per Cent	Fat, Per Cent	Carbohydrate, Per Cent
Bread	9 8	0 3	53 5
Butter		85 0	
Sugar			100 0
Milk	3 1	3 5	4 7

This is very similar to the small breakfast allowed the Boy Scouts in Papers 12[3] and 27[4] of this series In some of the experiments the subject took the food while in the calorimeter after two basal periods, in some the meal was taken at home shortly after rising

TABLE 2—Standard Breakfast—Summary Table

Subject	Sex	Age	Wt, Kg	Ht, Cm	Total Calories Direct	Total Calories Indirect	Cal per Sq M per Hr Basal	Per Cent Relation to Av Normal	Remarks
J C F	♂	23	62 7	180	210 4	195 4	35 2		5 hours after standard breakfast
J C F	♂	23	62 8	180	141 8	142 3	39 5	−10	No breakfast
W H O	♂	29	66 5	170	209 2	196 1	36 1		5 hours after standard breakfast
W H O	♂	29	66 6	170	128 7	134 6	38 0	−4 5	No breakfast
D P B	♂	27	65 3	177	212 3	218 6	40 2		5 hours after standard breakfast
D P B	♂	27	65 1	177	142 9	145 8	40 0	+1	No breakfast
D P B	♂	27	65 3	177	217 8	224 1	41 2		15 minutes after standard breakfast
E F D B	♂	34	73 9	179	228 5	*	40 1	+1	No breakfast
E F D B	♂	34	73 5	179	232 4	233 3	41 0		15 minutes after standard breakfast
L O'R	♀	25?	45 8	156	106 5	104 8	37 0	00	No breakfast
L O'R	♀		45 8	156	106 6	113 7	40 1		15 minutes after standard breakfast



Graphic demonstration of change in the level of metabolism following the ingestion of the standard breakfast The lines are drawn for each experiment according to the percentage deviation from the individual's own basal metabolism (Line O)

3 Du Bois, E F Clinical Calorimetry, Paper 12, The Metabolism of Boys Twelve and Fourteen Years Old Compared with the Metabolism at Other Ages, The Archives Int Med, 1916, **17,** 887

4 Immediately following this paper

DISCUSSION OF RESULTS

Although the series of experiments is not as large as might be desired, one point is clearly demonstrated, and that is the small and transient character of the rise in metabolism following a small breakfast During the first hour after the ingestion of the food the increase was 12 per cent in one case and 5 and 6 per cent in the others In the second hour the average was 2 per cent, in the third hour 2 per cent, and in the sixth, seventh and eighth hours the figures were actually 0 2 per cent lower than in the fasting, basal hours It is doubtful if a difference of 2 per cent is of any significance, because in basal experiments the results in hourly periods often show greater divergence No experiments were made more than eight hours after the standard breakfast, but there is no reason to suppose that there would be a delayed rise in metabolism after a small meal No such phenomenon has been seen in experiments on the specific dynamic action after large meals

The standard breakfast contained approximately 222 calories, enough to supply the basal energy requirement of the subjects three to four hours When the breakfast was taken at home and the subjects traveled to the laboratory their metabolism was, perhaps, double the basal figures In either case the food or its equivalent was all oxidized within a few hours, and it is perfectly natural that there should be little or no specific dynamic action after the complete utilization of the food It is obvious that we can determine the level of the basal metabolism within six hours of the taking of the standard breakfast described above The experimental conditions are made much easier for the subject, and it is believed that better results will be obtained Some may object to using the term "basal" for results obtained unless the subject is "breakfastless" or "nuchtern," since the original conditions demanded that a period of twelve to sixteen hours must have elapsed since the last meal On the other hand, no attention was previously paid to the size of that meal, and it is not impossible that there may be some specific dynamic action fourteen hours after a heavy protein dinner

This brings us to the economic question as to whether it is better to take two or three large meals a day or to divide the food into five or six small meals Judging from the results of the present experiments, the frequent meals, just supplying the energy as it is required would diminish the specific dynamic action and result in a saving equivalent to, perhaps, 5 or 10 per cent of the basal metabolism, or about 200 calories a day Practically, it would be of little importance since some of the specific dynamic action of the food is utilized in the increased metabolism of work In this connection it is well to recall

that Karl Thomas found that he could establish a lower nitrogen minimum if he took his protein food in nine small doses instead of taking it in three meals On the other hand, we must remember the waste of time in taking frequent meals and the tendency to overeat

SUMMARY AND CONCLUSIONS

Ten experiments were made on five subjects to determine the extent of the rise in metabolism following a small meal The standard breakfast used in all observations consisted of 30 gm bread, 8 gm butter, 10 gm sugar, and 60 c c milk, amounting to 4 7 gm protein, 9 0 gm fat, and 28 9 gm carbohydrate, or 222 calories In the first hour following the ingestion of this the heat production increased on an average 7 per cent , in the second hour, 2 per cent , in the third hour, 2 per cent In the sixth, seventh and eighth hours the metabolism was slightly lower than before the breakfast It is evident that when this small amount of food is taken for breakfast it is only during the first hour that the absorption of food could have been in sufficient quantity to produce the condition of a "metabolism of plethora"

477 First Avenue

CLINICAL CALORIMETRY

TWENTY-SEVENTH PAPER

METABOLISM OF BOYS TWELVE AND FOURTEEN YEARS OLD *

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AND
EUGENE F DU BOIS, M D
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The question of the effect of age on heat production was discussed in Paper 12 of this series[1] and the curve was drawn showing that metabolism is relatively high in childhood, falls rapidly during adolescence, then decreases slowly during the rest of life In Paper 19[2] it was shown that the curve needed slight alteration in extreme old age

At the time the Boy Scouts were first studied, in March and April, 1915, it was hoped that the same boys could be studied every year in order to plot a curve for each individual Unfortunately, this was impossible in 1916, and it was not until March and April, 1917, that the boys could be observed again in the calorimeter As will be seen from the accompanying charts, the changes in metabolism of the individual boys correspond so closely with the chart made two years ago that it is not necessary to alter the curve or change the conclusions made at that time

All of the boys examined in 1915 were studied in 1917 under experimental conditions which were practically unchanged With the exception of J D D B they came in from nearby suburbs on the morning of the observation All but one of the boys took a breakfast consisting of a glass of milk and a slice of toast, with butter, between the hours of half past 6 and half past 7 in the morning

The histories of the boys during the last two years are given below

F R S, aged 14 years, 11 months, has been perfectly well during the last two years except for earache with purulent discharge in 1916 He has grown 14 cm His voice has not yet changed, sex organs of moderate size, pubic hair fairly

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* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical Division of Bellevue Hospital

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1 Du Bois, E F Clinical Calorimetry, Paper 12 The Metabolism of Boys 12 and 13 Years Old Compared with the Metabolism at Other Ages THE ARCHIVES INT MED, 1917, **17**, 887

2 Aub, J C, and Du Bois, E F Clinical Calorimetry, Paper 19 The Basal Metabolism of Old Men THE ARCHIVES INT MED, 1917, **19**, 823

TABLE 1—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period	Carbon Dioxid, Gm	Oxygen, Gm	R Q	Water, Gm	Urine N per Hour, Gm	Indirect Calorimetry, Cal	Heat Eliminated, Cal
F R S	Prelim	12 15							
4/5/17 42 61 Kg 1 37 Sq M	1	1 15	23 01	20 29	0 825	38 52	0 470	67 66	68 39
	2	2 15	23 63	20 46	0 840	36 70	0 470	68 59	68 18
	Aver		23 32	20 38	0 832	37 61	0 470	68 13	68 28
J D D B	Prelim	11 46							
3/30/17 45 53 Kg 1 52 Sq M	1	12 46	22 56	21 84	0 751	39 69	0 501		75 85
	2	1 46	25 22	21 67	0 846	37 42	0 501		76 77
	Aver		23 89	21 75	0 798	38 55	0 501	72 2	76 31
Raymond M	Prelim	12 20							
3/27/17 49 09 Kg 1 24 Sq M	1	1 20	18 59	15 78	0 858	26 43	0 441		55 98
	2	2 20	19 43	16 67	0 848	24 95	0 441		56 51
	Aver		19 01	16 22	0 853	25 69		54 4	56 24
Reg F	Prelim	12 20							
3/28/17 48 55 Kg 1 52 Sq M	1	1 20	18 42	17 77	0 754	27 27	0 483		58 07
	2	2 20	21 49	17 82	0 877	28 68	0 483		60 64
	Aver		19 95	17 79	0 815	27 97	0 483	59 1	50 35
Harry B	Prelim	2 09							
3/29/17 49 09 Kg 1 51 Sq M	1	2 39	10 84	9 58	0 822	17 59	0 423		34 32
	2	3 39	21 50	19 94	0 784	38 45	0 423		70 86
	Aver		-16 17	14 76	0 803	28 02	0 423	65 3	52 59
Henry K	Prelim	12 22							
4/2/17 49 29 Kg 1 34 Sq M	1	1 22	22 23	19 82	0 816	27 88	0 330		61 83
	2	2 22	22 60	19 96	0 824	30 20	0 330		67 16
	Aver		22 41	19 89	0 820	29 04	0 330	66 6	64 49
Arthur A	Prelim	11 18							
4/3/17 39 46 Kg 1 37 Sq M	1	12 18	20 85	18 67	0 812	26 18	0 367		65 73
	2	1 18	20 79	18 26	0 828	24 97	0 367		64 87
	Aver		20 82	18 46	0 825	25 57	0 367	61 8	65 30
Leslie B	Prelim	11 23							
3/29/17 34 20 Kg 1 20 Sq M	1	11 53	9 67	8 64	0 814	13 50	0 513		29,70
	2	12 53	18 90	15 00	0 916	26 53	0 513		55 62
	Aver		14 29	11 82	0 865	20 01	0 513	53 1	42 70

—CALORIMETER DATA

Direct Calorimetry (Rectal Temp), Cal	Rectal Temp , C	Average Pulse	Work Adder, Cm	Non protein R Q	Per Cent Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd	Per kg	Per Sq M (Linear)	
	37 09									Basal
62 31	36 93	76	13							Quiet, reading 50 min
69 29	36 97		16							Quiet, reading 20 min
65 80	36 99		14	0 84	18	45	37	1 60	49 7	
	37 33	77								Basal, not very satisfactory, excluded from averages and chart
61 82	36 97	72	10							
84 01	37 17	84	16							Third period started, removed from calorimeter because of pain in leg
72 91	37 16	77	13	0 80	18	57	25	1 59	47 5	
	37 12	68								Basal
52 94	47 03		3							Motionless
55 10	36 99	78	3							Motionless
54 02	37 05	73	3	0 87	21	36	43	1 11	43 9	
	36 99									Basal
50 48	36 81		8							Quiet, asleep 20 min
56 28	36 71	63	9							Quiet
53 38	36 84		8	0 82	22	48	30	1 22	39 1	
	37 33									Basal
28 40	37 19	75	4							Reading 5 min , very quiet
59 44	36 92		3							Very quiet
43 92	37 15		3	0 80	17	58	25	1 33	43 2	
	36 99	71								Basal
53 74	36 80	75	5							Very quiet, reading 8 min
69 71	36 87	72	2							Very quiet, reading 60 min
61 72	36 89	73		0 82	13	63	24	1 35	43 3	
	36 98									Basal
56 91	36 72		8							Very quiet, reading 20 min
63 36	36 68	82	11							Very quiet, reading 50 min
60 13	36 79		9	0 83	16	50	34	1 57	45 1	
	37 19									Basal
26 75	37 09		5							Very quiet
50 18	36 91	65	15							Somewhat restless
38 46	37 06		10	0 91	26	23	51	1 55	44 3	

TABLE 2—SHOWING THE RELATION BETWEEN THE BASAL METABOLISM AND THE INCREASE—

Name	First Experiment		Second Experiment		Weight in Kg			Height in Cm			Calories per Hour		
	Age, Years	Signs of Puberty	Age, Years	Signs of Puberty	First Exper	Second Exper	Increase in per Cent	First Exper	Second Exper	Increase in per Cent	First Exper	Second Exper	Change in per Cent
L B	13 3/12	±	14 3/12	++	28 5	34 2	20	141	151	7	54 1	53 1	— 2
R M	12 6/12	0	14 6/12	±	30 4	49 1	61	141	149	6	59 0	54 4	— 8
R F	12 8/12	+	14 8/12	+++	35 4	48 6	38	148	166	12	61 8	59 1	— 4
F R S	12 10/12	0	15	+	32 1	42 6	33	142	156	10	58 6	68 1	+18
A A	13 8/12	0	15 8/12	+	30 6	39 5	29	147	160	9	56 1	61 8	+10
H B	13 10/12	++	15 10/12	+++	36 6	49 1	34	146	162	11	58 4	65 3	+12
H K	13 11/12	±	15 11/12	++	36 0	49 3	37	148	166	12	60 0	66 6	+11
Aver					32 8	48 1	46	145	159	10	58 3	61 2	+ 5

abundant During the experiment he was quiet This boy took a somewhat larger breakfast than the others At 7 a m he had two slices of toast and a cup of coffee with sugar and cream

J D D B, aged 14 years, 2 months, has been perfectly well during the last two years and has grown 16 cm His voice is just beginning to change, genitalia about one-half adult development, pubic hair about one-quarter present, scant hair in axillae, slight down on lip

The experiment of this boy was not satisfactory He tried so hard to keep quiet that he developed a severe cramp in the leg He was in great pain, especially during the second period This probably accounts for his relatively high metabolism The results are not used in the averages and are not shown on the graphic chart

Raymond M, aged 14 years, 7 months, has grown only 8 cm His health has been good His voice has not yet changed, genitalia are just beginning to develop, pubic hair scant, a few axillary hairs are present, no down on lip During the experiment he was motionless

Reginald F, aged 14 years, 8 months, has grown 18 cm Two weeks before the observation he had a mild attack of cramps in the abdomen, otherwise well Three months prior to the observation he had to stop singing in a choir on account of change in voice Genitalia are adult in type, pubic hair is abundant, and there is a slight growth of down on the lip During the observation he was quiet

Harry B, aged 15 years, 10 months, has grown 15 5 cm His health has been good The voice and genitalia are of adult type, pubic and axillary hair abundant, slight down on lip During the observation he was quiet

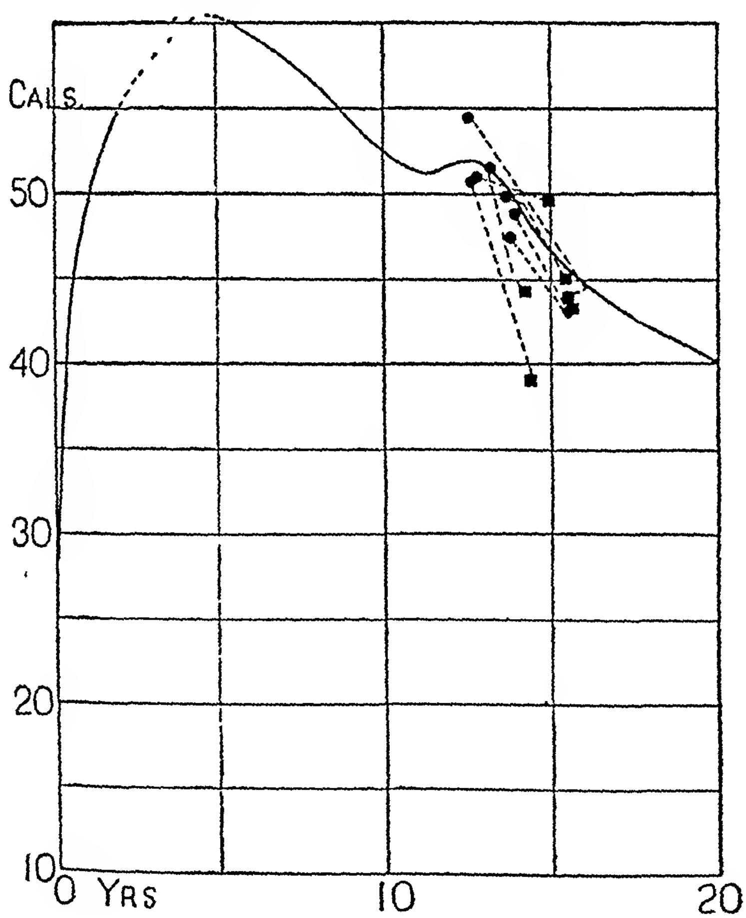
Henry K, aged 15 years, 11 months, has grown 18 cm His health has been good His voice is changing, genitalia are about three-quarters adult development, pubic hair all present, axillary hair about one-half present, slight down on lip He was very quiet during the experiment

Arthur A, aged 15 years, 8 months, has grown 13 cm Although small and slight he has won a medal as the best all-round Boy Scout in his troop During the last two years he has been perfectly well The voice has not yet changed, genitalia are about one-quarter way toward adult development, no hair in axillae or on lip Both mammary glands are palpable, about 1 cm in diameter, they are not tender He was very quiet during the observation

Leslie B, aged 14 years, 3 months During the last two years he has gained 10 5 cm and has been perfectly well except for a broken finger and a dog bite

Calories per Sq M Surface per Hour			Calories per Kg per Hour		Average R Q		Circumference of Thorax		Surface Area (Linear Formula)		Average Pulse	
First Exper	Second Exper	Decrease in per Cent	First Exper	Second Exper	First Exper	Second Exper	First Exper	Second Exper	First Exper	Second Exper	First Exper	Second Exper
							Cm	Cm	Sq M	Sq M		
51 6	44 3	—14	1 90	1 55	0 82	0 87	61 8	67 5	1 05	1 20	88	65
54 4	43 9	—19	1 94	1 11	0 81	0 85	65.8	68 5	1 08	1 24	85	73
50 7	39 1	—23	1 75	1 22	0 94	0 82	68 2	76 6	1 22	1 52	79	63
51 0	49 7	— 3	1 79	1 60	0 83	0 83	66 2	73 0	1 12	1 37	80	76
49 9	45 1	—10	1 84	1 57	0 78	0 82	65 4	71 0	1 13	1 37	81	82
47 4	43 2	— 9	1 60	1 33	0 86	0 80	71 4	80 2	1 23	1 51	88	75
48 8	43 3	—11	1 66	1 35	0 86	0 82	67 7	77 3	1 22	1 54	87	73
50 6	44 1	—13										

His voice is beginning to change, genitalia about one-half developed, pubic hair about one-half present, scant hair in axillae, no down on lip During the first hour of observation he was very quiet, during the second, somewhat restless



Reproduction of original age curve showing relationship of findings to the line drawn in 1915 Each round dot represents the calories per square meter per hour for the boy in 1915 A dash line connects it with the square which represents the result obtained in 1917

DISCUSSION OF RESULTS

The results are shown graphically in the chart All of the individuals show a marked decrease in metabolism In the case of F R S this is not as striking as in the others Although the majority of the boys come a little below the line that was drawn two years ago, the change is not great enough to make it advisable to draw a new curve The important fact remains that there is a rapid fall in metabolism during adolescence The average decrease for the seven satisfactory cases studied is 13 per cent Their average metabolism at the ages of 14 and 15 years is 44 1 calories per square meter per hour, which is 11 per cent above the average for adult men between the ages of 20 and 40 years

In the three youngest boys the metabolism during the twelfth year was actually greater in calories produced than during the fourteenth year, although the boys showed a gain in weight of between 35 and 50 per cent

477 First Avenue

CLINICAL CALORIMETRY

TWENTY-EIGHTH PAPER

THE METABOLISM IN MALARIAL FEVER*

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(WITH THE TECHNICAL ASSISTANCE OF G F SODERSTROM)
NEW YORK

I INTRODUCTION

When the respiration calorimeter of the Russell Sage Institute of Pathology was originally planned one of the main problems in view was the study of the rise and fall of the body temperature in fever For the first time it became possible to measure in the clinic practically all the factors which would tell the story as to what was taking place within the body The preliminary work that was done in typhoid fever, with its comparatively slow changes in body temperature, demonstrated the extraordinary difficulty of the technic One case of malaria studied that same year gave warning of the troubles to be encountered when the temperature fluctuations were rapid It was for this reason that the main study of malaria was postponed until the calorimeter staff had been drilled four years and the technic and apparatus so improved that the problem seemed capable of solution

The calorimeter is a bulky apparatus and does its best work when the metabolic condition of the patient remains unchanged from hour to hour With the onset of the malarial chill there is an abrupt change in the patient's metabolism and the calorimeter must be rapidly adjusted to meet the new conditions Again, at the termination of the chill there is another change, and at the outbreak of sweat a new set of conditions is encountered In previous years it had been the custom to make the periods of observation one hour in length, and even these periods kept the staff busy This year it was found possible to obtain satisfactory results in periods as short as half an hour, and in some instances twenty-two minutes In this manner one could study different portions of the malarial chill, whereas the one-hour periods would necessarily have included two or three different phases of the paroxysm

The problems were to determine the influence of fever on the level of heat production, and to see whether the latter is proportional to the

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* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical Division of Bellevue Hospital

height of the temperature, or if the height of the temperature depends on the level of the metabolism Even more important was the study of the mechanism by which the body raises or lowers its temperature Does the temperature rise because the heat production has been increased or because the heat elimination has been diminished, or from a combination of these two causes? Does the body temperature fall because the heat production is diminished, or because the heat elimination is increased, or, again, from a combination of the two? Still another problem is the measurement of the average temperature change within the body Hitherto our knowledge of the temperature change has been dependent on thermometers in the mouth, rectum or axillae Another interesting problem was the comparison of the temperature regulation during malarial chill and the chills following the intravenous injection of a foreign protein Finally, there remained the interesting question as to the character of the foodstuffs oxidized during a chill

II THE MECHANISM OF THE RISE AND FALL OF TEMPERATURE

Any change in body temperature is due to a disturbed relation between two factors, heat production and heat elimination Heat production is the result of the combustion of foodstuffs within the body If the body is to remain at a constant temperature, the heat thus produced must be eliminated This is accomplished chiefly by two avenues of heat loss first, radiation and conduction of heat to the surrounding air, and second, the vaporization of water eliminated from the skin and lungs Every gram of water which is vaporized at 23 C absorbs 0 584 of a calory Ordinarily in afebrile conditions the heat lost in the vaporization of water constitutes about one quarter of the total heat eliminated A slight amount of heat is lost in the urine and feces and in warming food and drink which is introduced into the body at a low temperature The other three quarters, however, is lost chiefly by radiation and conduction In afebrile conditions the heat production equals the heat elimination, thus keeping the body temperature at a constant level

We must decide whether fluctuation in temperature is due to a change in heat production or in heat elimination A theoretical consideration of the problem would indicate that both must be affected

To raise 1 kg of water 1 degree C requires one calory of heat To raise 1 kg of body tissue 1 degree C requires only 0 83 calory In other words, the specific heat of the body is said to be 0 83 If, therefore, the temperature of a man weighing 70 kg should rise 1 degree C within an hour, 70 × 0 83 or 58 1 calories would necessarily be stored in that man's body The ordinary heat production of the man at rest would be about 70 calories per hour If there were no increase in heat

production only 119 calories, or about a sixth of the usual amount of heat, would be eliminated This does not seem probable

On the other hand, it is a well known fact that heat production is enormously increased during severe exercise, such as mountain climbing or running, or during shivering after exposure to cold With this increase in metabolism, however, there is no marked rise in temperature After the ingestion of large amounts of protein food the heat production may be increased 50 per cent or more, and yet there is no rise in body temperature The explanation is that in these conditions the heat elimination is increased to compensate for and to equal the extra heat production Thus, it would appear that there is in fever some disturbance in the power of the body to eliminate heat

The problem, therefore, is to determine how much and in what manner each of these factors acts to produce changes in body temperature

Much careful work has been done on this problem with quite conflicting results Traube,[1] as long ago as 1863, studied the question of the mechanism of fever He attributed the cause of fever to a sudden contraction of the peripheral blood vessels which prevented the proper distribution of blood to the surface of the body and thus interfered with a normal heat loss Those who followed Traube's teaching believed that the cause of fever was not an increase in heat production, but a decrease in heat elimination Senator[2] believed that the rise in body temperature took place in consequence of an abnormally high heat production with a heat elimination not correspondingly high Senator thus assumed an increase in the production of heat which Traube did not find Leyden[3] found a considerable increase in heat production

All of the earlier workers were handicapped by imperfect and incomplete apparatus The problem could not be finally settled except by an instrument which very accurately measured heat production and respiratory exchange simultaneously in short periods This has been possible for the first time with the calorimeter of the Russell Sage Institute of Pathology Using this instrument in their observations on typhoid fever, Coleman and Du Bois[4] found that an increase in heat production accompanied a rising body temperature in six out of seven cases observed The heat elimination was not equal to the heat production, but rose to meet the higher level of metabolism One observa-

1 Traube Allg med Centr-Ztg, 1863, **32,** 410, 426 and 810

2 Senator Allg med Centr-Ztg, 1868, **37,** 926, Untersuchungen uber die fieberhaften Prozesse, Berlin, 1873

3 Leyden Deutsch Arch f klin Med, 1870, **7,** 536

4 Coleman, W, and Du Bois, E F Clinical Calorimetry, Paper 7, Calorimetric Observations on the Metabolism of Typhoid Patients With and Without Food, The Archives Int Med, 1915, **15,** 887

tion showed a decrease in both heat production and heat elimination These observers also found that when the body temperature is constant at high fever the heat production and heat elimination are equal to each other When the body temperature falls the heat elimination rises above the heat production, while the amount of the latter may or may not fall

The fluctuation of temperature in the typhoid cases was not striking, the maximum change being only 0 7 C The present work deals with more rapid and with greater changes and should, therefore, yield more decisive results

III REVIEW OF LITERATURE

The first of the conditions to be considered is malarial fever Some very important work has previously been done on the metabolism of this disease

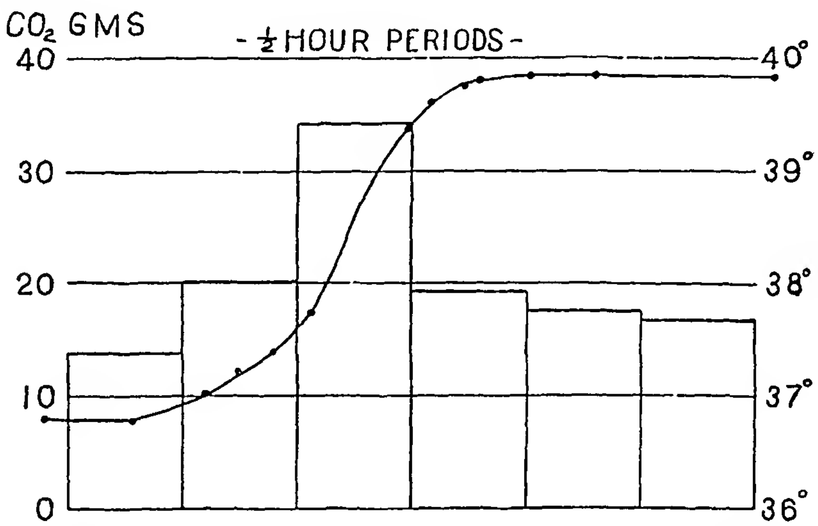

Fig 1—Curved line shows the body temperature and the columns the carbon dioxid elimination of Liebermeister's patient during a malarial paroxysm

In 1870 Liebermeister[5] studied the carbon dioxid output of two patients before, during and after a malarial chill He considered that the carbon dioxid expired accurately indicated the heat production How correct this supposition was can be judged by comparison of the chart given by Liebermeister with our record of the patient George S (page 633) Liebermeister demonstrated that the chill is accompanied by a great increase in heat production Following the chill the heat production drops to a level not far above that observed before the paroxysm began He believed that the level of heat production is only slightly dependent on the absolute height of the body temperature A glance at the accompanying chart (Fig 1) will show that this is true During the rapid rise of temperature accompanying the chill there is a great increase in the production of carbon dioxid

5 Liebermeister Deutsch Arch f klin Med, 1871, 7, 153

After the chill the temperature continues to rise although the heat production suddenly drops nearly to its former level Liebermeister very aptly compares this to the action of the sun on the temperature of the air on the earth's surface The sun, which would correspond to the heat production, exerts its maximum heat at midday During this period the temperature of the air rises rapidly After noon, although the heat of the sun becomes less intense, the temperature of the air continues to rise for a considerable period and remains high even when the sun is set

The first calorimetric observations of a patient with malaria were made in 1892 by Isaac Ott[6] of Philadelphia, who used an instrument which required a plus correction of 16 per cent He found during a chill a great increase in heat production, with a considerable decrease in heat elimination He also confirmed Liebermeister's finding that following the chill the heat production falls, although the temperature still remains high During the fall in temperature he found a great increase in heat elimination and in the elimination of water, without marked change in the heat production

Probably the best known work on the rise and fall of temperature in malaria was done by Likhatscheff and Avroroff[7] in 1902 As excellent abstracts of this most important research have been made by Ott[6] and by A I Ringer,[8] it will not be necessary to review the details of their methods They used a large Paschutin calorimeter with which they measured both the heat production by the direct method and the carbon dioxid output Their results are most interesting and important They found that an increase in heat production occurred during a rise in temperature, an increased heat elimination and output of water during the fall The output of carbon dioxid increased greatly during the rise in temperature but lagged behind the maximum heat production They concluded that a rise in body temperature depends on an increased heat production

IV METHODS OF INVESTIGATION

In the following experiments the calorimeter of the Russell Sage Institute was employed This has been described in Paper 2 of this series[9] The heat production was measured by both direct and indirect

6 Ott, Isaac Fever Its Thermotaxis and Metabolism, New York, 1914

7 Likhatscheff and Avroroff Investigations of Gaseous and Heat Exchange in Fevers Report of the Imperial Military Academy, St Petersburg, 1902, **5,** Parts 3 and 4 We are indebted to Dr F G Benedict of the Carnegie Nutrition Laboratory for permission to consult his translation of this work

8 Ringer, A I Physiology and Pathology of Fever, Am Jour Med Sc, 1911, **142,** 485

9 Riche, J A, and Soderstrom, G F Clinical Calorimetry, Paper 2, The Respiration Calorimeter of the Russell Sage Institute of Pathology in Bellevue Hospital, The Archives Int Med, 1915, **15,** 805

methods, the factors of which have nothing in common The direct method measures the heat lost in radiation and conduction directly The vaporized water is collected and weighed and, therefore, the heat lost in this manner can easily be calculated Heat lost by radiation and conduction and in the vaporization of water together indicate the total heat elimination If the heat gained or lost by the body for any given period be added to or subtracted from the heat eliminated the actual amount of heat production can be determined Unfortunately, the heat change of the body is dependent on the measurement of the rectal temperature which, although the best method at our disposal, does not accurately indicate the heat of the entire body Direct calorimetry, therefore, in short periods, especially in fever, does not accurately represent the true heat production Over sufficiently long periods in afebrile conditions it is a satisfactory method and agrees with the heat as determined by the indirect method It is on this method of indirect calorimetry that one should place the chief reliance in short periods This has been fully described in the first paper of this series [10]

In many of the older instruments the production of carbon dioxid alone was measured In the more accurate of these this determination gives a fairly good index of the height of metabolism

A consideration of the respiratory quotients is important in studying the mechanism of the rise and fall of temperature, as they indicate the kinds of foodstuffs burned in the body It has been noted that during shivering glycogen is burned rapidly [11] If this be true the quotients should be high during a chill

Another problem that can be considered during these studies is the relation of the heat lost in the vaporization of water to the total heat production In previous work on this problem the heat of vaporization has always been considered in relation to the total heat produced rather than to the heat eliminated In afebrile conditions the heat production and the heat elimination are equal It does not matter, therefore, to which the heat of vaporization is compared In fluctuations of fever, however, the heat production and heat elimination are unequal It will be interesting to determine whether the amount of heat lost in vaporizing water follows the level of heat production or that of heat elimination

HISTORIES OF PATIENTS

CASE 1—Victor J, tertian malaria

History—A fireman, born in Sweden, 24 years of age He was admitted April 6, 1913, discharged cured April 19, 1913 He lived in the South during

10 Lusk, Graham Clinical Calorimetry, Paper 1, A Respiration Calorimeter for the Study of Disease, THE ARCHIVES INT MED, 1915, **15,** 793

11 Lusk, G The Influence of Cold Baths on the Glycogen Content of Man, Am Jour Physiol, 1911, **27,** 427

the year preceding (October, 1912) and had malaria continually Since that time he has been in New York and has had no trouble until the present attack He drinks an occasional glass of beer He denies venereal infection

For one week preceding admission he did not feel well, but continued work until April 4, when he had a severe chill, followed by high fever and sweating He was able to work the following day but on the 6th had another chill which brought him to the hospital

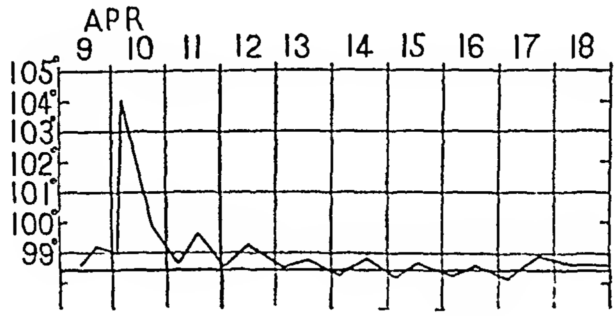

Fig 2—Temperature chart of Victor J

Physical Examination—A medium sized, well nourished young man Spleen is palpable two finger breadths below costal margin On lips and nasal margin there is well marked herpes

The urine is negative Blood pressure systolic, 120 mm , diastolic, 50 mm Blood hemoglobin, 90 per cent , leukocytes, 9,400, polynuclears, 64 per cent , malarial organisms, present (tertian type)

He was observed in the calorimeter on April 10 from 8 30 to 11 30 a m Quinin was started on the 11th and was continued until the day of discharge, April 19

Case 2—George S , tertian malaria

History—A seaman, born in Sweden, 19 years of age He was admitted March 12, 1917, discharged cured March 22, 1917 In October, 1915, he had gonorrhea which cleared up in six weeks without complications In June, 1916, he again had a urethral discharge which lasted until October In September,

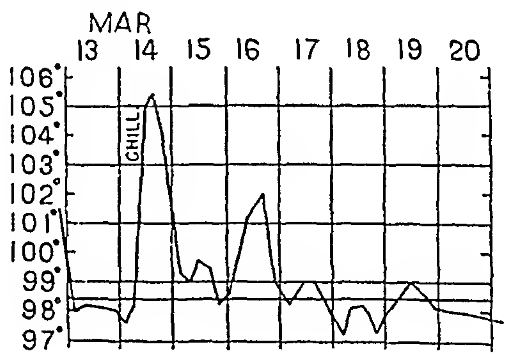

Fig 3—Temperature chart of George S

1916, his occupation took him to South America where he contracted malaria He was treated on his return to New York in St Vincent's Hospital, where he had several chills Malarial organisms were found and, after some quinin treatment, he was sent to Bellevue Hospital While in Bellevue (October) he ran a high, extremely irregular, intermittent fever with no chills, had a moderately enlarged spleen and was very anemic Erythrocytes, 1,500,000, hemoglobin, 35 per cent , leukocytes, 4,000, lymphocytes, 70 per cent After quinin treatment the temperature became normal and the anemia gradually disappeared

TABLE 1—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period	Carbon Dioxid, Gm	Oxygen, Gm	R Q	Water, Gm	Urine N per Hour, Gm	Indirect Calorimetry, Cal	Heat Eliminated, Cal
Victor J 4/10/13 69 6 Kg 1 98 Sq M *	Prelim	8 28							
	1	9 28	41 2	39 6	0 76	32 5	0 75	130 2	143 7
	2	10 28	39 2	36 5	0 78	33 1	0 75	120 5	145 2
	3	11 28	38 1	35 9	0 77	32 8	0 75	118 3	122 5
Victor J 4/16/13 64 0 Kg *	Prelim	9 45							
	1	10 45	23 7	24 0	0 72	27 0	0 47	78 2	71 9
	2	11 45	23 4	23 0	0 74	29 4	0 47	75 3	78 7
	3	12 45	25 9			29 2	0 47		80 6
	4	1 45	27 1	27 1	0 72	32 1	0 47	88 4	88 1
George S 3/14/17 71 7 Kg 1 83 Sq M	Prelim	11 18							
	1	11 48	13 8	12 7	0 79	19 0	0 55	42 0	36 3
	2	12 18	13 9	13 3	0 76	18 1	0 55	43 9	37 7
	3	12 40	12 3	10 1	0 88	12 1	0 55	34 2	25 5
	4	1 20	53 5	45 0	0 86	28 8	0 55	153 1	53 7
	5	2 20	43 6	39 5	0 80	48 7	0 55	131 9	91 1
	6	3 20	39 3	37 5	0 76	50 2	0 55	123 9	99 9
Paul K 3/16/17 57 4 Kg 1 63 Sq M	Prelim	12 35							
	1	1 35	25 1	23 1	0 79	38 6	0 58	76 6	78 9
	2	2 35	26 1	24 8	0 77	38 2	0 58	81 9	80 8
Paul K 3/17/17 58 1 Kg 1 63 Sq M	Prelim	10 07							
	1	11 07	26 1	24 0	0 79	38 2	0 56	79 3	87 3
	2	12 17	29 0	28 0	0 75	60 9	0 56	92 0	113 5
	3	1 07	21 8	19 5	0 82	47 4	0 56	65 0	78 2
	4	2 07	26 2	24 3	0 79	47 3	0 56	80 2	89 8
	Aver							79 1	
Paul K 3/20/17 56 5 Kg 1 63 Sq M	Prelim	7 50							
	1	8 50	25 3	23 9	0 77	31 9	0 73	78 2	73 6
	2	9 50	24 6	22 8	0 79	31 1	0 73	75 1	79 5
	3	10 50	25 8	24 0	0 78	33 7	0 73	78 9	82 0
Fred E 3/23/17 56 7 Kg 1 65 Sq M	Prelim	2 02							
	1	3 02	22 4	20 0	0 81	39 0	0 40	66 6	69 4
	2	4 02	24 0	22 0	0 79	39 1	0 40	72 9	73 2
Sam F † 4/11/17 59 5 Kg	Prelim	12 27							
	1	1 29	25 4	23 6	0 78	40 0	0 30	78 3	80 2
	2	2 34	59 0	63 5	0 63	63 1	0 30		111 3
Sam F 4/12/17 60 6 Kg 1 70 Sq M	Prelim	3 43							
	1	4 43	30 9	28 3	0 79	68 3	0 42	94 3	111 3

—Calorimeter Data

Direct Calorimetry (Rectal Temp), Cal	Rectal Temp , C	Average Pulse	Work-Adder, Cm	Non protein R Q	Per Cent Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd	Per Kg	Per Sq M (Linear)	
	40 5									Falling temperature
124 0	40 1			0 75	15	73	12	2 01	65 7*	Used Meeh's formula
120 5	39 6			0 78	17	63	20	1 86	60 9*	
101 1	39 2			0 77	17	66	17	1 83	59 7*	
	37 1									Afebrile
71 5	37 1			0 70	16	84		1 22	39 7*	
75 5	37 0			0 73	17	77	6	1 18	38 2*	
84 9	37 1									
85 1	37 0			0 72	14	83	3	1 38	44 8*	
	37 3									Observation on chill
38 9	37 3	76	2	0 79	17	60	23	1 18	44 9	Motionless
46 7	37 5		7	0 75	17	71	12	1 22	48 0	Quiet, turned once
50 8	37 9	96	5	0 88	15	27	58	1 30	51 0	Quiet, mild, shivering last two minutes
168 7	39 9		4	0 87	6	42	52	3 20	126 0	Quiet except for chill, chill 12 41 to 1 15
161 3	41 2	100	19	0 80	11	62	27	1 84	72 1	Quiet except last min
93 4	41 1		8	0 76	12	69	19	1 73	67 7	Very quiet
	37 7									Afebrile
76 6	37 7	77	6	0 78	20	60	20	1 34	47 0	Very quiet
79 9	37 7	75	15	0 75	19	68	13	1 46	50 2	Fairly quiet
	38 5									Falling temperature
82 9	38 5	80	13	0 80	19	57	24	1 36	48 7	Fairly quiet
103 1	38 3	77	16	0 74	19	73	18	1 35	56 4	Fairly quiet, coughed
65 1	38 0	75	13	0 83	19	48	33	1 34	39 9	Fairly quiet
79 8	37 9	78	16?	0 79	19	58	23	1 38	49 2	Quiet
	38 4									Fever after chill
72 2	38 2	81	13	0 76	24 9	61	13 6	1 38	47 9	Very quiet
78 2	38 2	77	8	0 78	25 9	55	18 5	1 33	46 1	Very quiet
77 9	38 1	74	15	0 78	24 0	57	17 9	1 40	48 4	Fairly quiet
	36 9									Afebrile
57 7	36 7	56	10	0 82	16	52	32	1 18	40 3	Fairly quiet
75 7	36 7	56	11	0 79	15	60	25	1 29	44 2	Fairly quiet
	37 3	52								Before chill
84 2	37 4		19	0 78	11	66	23	1 27	41 6	Slept 15 min , slightly restless
223 9	39 7		27							Quiet except for chill, chill 1 48 to 2 25
	39 1									Falling temperature
88 3	38 7	84	16	0 79	12	62	26	1 56	55 5	Quiet, during last 15 min humidity in calorimeter rose rapidly

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period	Carbon Dioxid, Gm	Oxygen, Gm	R Q	Water, Gm	Urine N per Hour, Gm	Indirect Calorimetry, Cal	Heat Eliminated, Cal
Sam F 4/13/17	Prelim	11 30							
60 5 Kg 1 70 Sq M	1	12 30	23 8	22 1	0 79	38 7	0 38	73 1	75 5
	2	1 30	24 7	23 2	0 77	37 8	0 38	76 7	77 3
	3	1 53	8 8	8 1	0 79	13 3	0 38	26 8	28 6
	4	2 18	11 1	10 9	0 74	13 8	0 38	35 8	31 1
	5	3 18	27 8	25 1	0 81	33 4	0 38	83 9	74 7
Sam F 1/30/17	Prelim	11 23							
61 9 Kg	1	12 23	22 4	19 5	0 84	29 3	0 43		65 4
	2	1 23	24 0	20 8	0 84	29 3	0 43		69 9
	Aver							67 5	

* Height not measured Used Meeh's formula
† Small amount of oxygen admitted from preliminary period At end of second period, sulphuric acid bubbled over into the sodium bicarbonate can, thus generating CO_2 and heat The indirect calorimetry is therefore worthless, also heat eliminated is unreliable This period is included to show the great amount of heat stored in the body during chill

He remained well until March 2, ten days before admission, when he again had chills, fever and sweats He had a chill every second day until admission to the hospital The last chill occurred on the morning of admission day

Physical Examination—A well developed, fairly well nourished boy, rather pallid Tongue shows faint white coat Heart Left border of dulness is in the fifth space 14 cm from the median line, right border, 3 cm from median line in fourth space There is a soft blowing systolic murmur at the apex, not transmitted Pulmonary second sound is accentuated Spleen Edge is indefinitely felt two finger breadths below the costal margin

The urine is negative Blood Erythrocytes, 3,250,000, hemoglobin, 60 per cent (Sahli), leukocytes, 4,200, polynuclears, 37 per cent, lymphocytes, 32 per cent Many malaria parasites (tertian) are found

On March 14 he was in the calorimeter He had a severe chill followed by an abrupt rise in temperature to 105 4 F On the 15th he was comfortable On the 16th he had a rise in temperature to 102 F, but no chill Quinin medication was started on the evening of March 16 and was continued until March 19 He had no further symptoms and was discharged on March 22

CASE 3—Paul K, malaria (aestivo-autumnal)

History—A laborer, born in Austria, 30 years of age He was admitted, March 11, 1917, to the service of Dr R J Carlisle, Bellevue Hospital, and was transferred to the Metabolism Ward March 15, 1917, discharged improved March 28, 1917 He drinks moderately of beer and whisky He denies venereal infection He came to this country in 1913 and worked in New York for one year He then moved to North Carolina Six months later he was seized with chills and fever which came every second day For eight days he was in a hospital On his discharge he returned to New York and has had no recurrence until the present time

On March 6 at 3 o'clock in the morning he was seized with fever and a slight chill During the following five days he had repeated chills and a constant, severe abdominal pain localized in the left hypochondrium over the spleen

Direct Calorimetry (Rectal Temp), Cal	Rectal Temp, C	Average Pulse	Work-Adder, Cm	Non protein R Q	Per Cent Calories from			Calories per Hour		Remarks
					tein	Fat	hyd	Kg	(Linear)	
	36 9									Time of expected chill
73 1	36 8	55	7	0 78	14	64	22	1 21	43 0	Very quiet, slept 15 min
77 8	36 8		15	0 77	13	69	18	1 27	45 1	Quiet
32 5	36 9		4	0 78	15	62	23	1 16	41 1	Quiet
35 5	37 0		5	0 73	12	82	6	1 36	50 7	Quiet, felt chilly 2 00 to 2 30 p m
87 4	37 3		12	0 81	12	58	30	1 39	49 4	Quiet, drank water
	36 9									Basal (after cure)
58 4	36 8	55								Very quiet, slept 15 min
69 0	36 7		2							Very quiet
				0 85	17	43	40	1 09	39 7	

Physical Examination—March 16, a moderately emaciated but well developed man, very pallid Mucous membranes very pale Herpes on both eyes and nose Tongue is moist and covered with a moderate white coat He coughs frequently A few râles are heard over both sides of the chest The spleen is felt as a soft edge at the costal margin Cervical, inguinal, epitrochlear and axillary lymph nodes are palpable

His urine is negative Blood pressure systolic, 110 mm, diastolic, 68 mm Sputum negative for tubercle bacilli

He had sharp rises in temperature on March 12 and 14 Neither during these exacerbations nor in those which followed did he have a chill He was in the calorimeter from 11 30 a m to 2 35 p m, March 16 At that time his

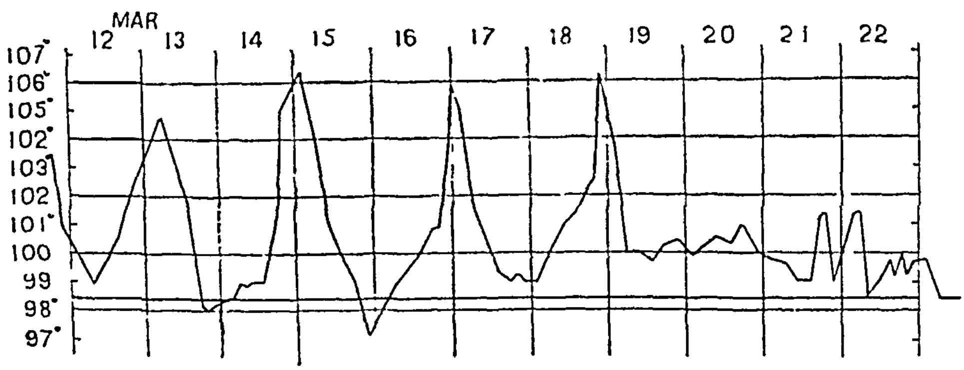

Fig 4—Temperature chart of Paul K

blood showed leukocytes, 4,000, erythrocytes, 2,700,000, hemoglobin, 55 per cent (Sahli), malarial parasites were found March 17, from 9 30 a m to 2 15 p m, he was again in the calorimeter On the 18th quinin sulphate, 20 grains, was given On the following day parasites were again found in the blood On the 20th he was observed in the calorimeter from 7 to 10 p m Quinin was started again on the 22d and was continued until the time of discharge, March 28 On the 22d leukocytes were 7,000, erythrocytes were 2,200,000, hemoglobin (Dare), 30 per cent, anisocytes and poikilocytes were present At the time of his discharge he had a normal temperature and had no complaints

TABLE 2—Calorimeter Data in Malaria

Subject and Date	Age	Period of Disease	Rectal Temp, C	Average Pulse	Average R Q	Indirect Calorimetry Average per Hour		Per Cent Divergence of Direct Cal from Indirect Cal	Per Cent Total Heat Elimination Lost in Vap of Water	Change in Rectal Temperature	Change in Average Body Temperature	Per Cent Rise Above Average Normal Basal for Age
						Calories per Kg	Calories per Sq M					
Paul K 3/10/17	30	Afebrile, between paroxysms	37 7 37 7	77	0 78	1 4	48 5	—1 0	29	±0 0	±0 0	+22
George S 3/14/17	19	Afebrile, one hour before severe chill	37 3 37 5	76	0 78	1 2	46 5	—0 2	29	+0 2	+0 2	+14
Sam F 4/11/17	32	Afebrile, one hour before severe chill	37 3 37 4	52	0 78	1 3	44 6	—7 0	29	+0 1	±0 0	+12
Sam F 4/13/17			36 9 36 9	55	0 78	1 2	43 7	+3 4	29	±0 0	—0 1	+ 9
Sam F 4/30/17	32	Afebrile, after treatment 17 days after last chill	36 9 36 7	55	0 84	1 1	39 7	—6 3	26	—0 2	±0 0	± 0
Fred E 3/22/17	18	Afebrile, after treatment 6 days after last chill	36 9 36 7	56	0 80	1 2	42 3	—5 0	32	—0 2	—0 1	± 0
Victor J 4/16/13	24	Afebrile, after treatment 6 days after last chill	37 1 37 0		0 72	1 3	41 2*	—4 8		—0 1	—0 1	+14
Paul K 3/20/17	30	Late falling temperature after end of last paroxysm	38 4 38 1	78	0 78	1 4	47 4	—1 8	24	—0 3	—0 2	+19
George S 3/14/17	19	Rising temperature before chill	37 5-37 9	96	0 88	1 3	51 0	+13 5	28	+0 4	+0 2	+24
George S 3/14/17	19	Chill	37 9 39 9		0 86	3 2	126 0	+9 3	31	+2 0	+1 7	+216
George S 3/14/17	19	Rising temperature after chill	39 9 41 2	100	0 80	1 8	72 1	+22 0	31	+1 3	+1 7	+76
George S 3/14/17	19	High constant temperature after chill	41 2 41 1		0 76	1 7	67 7	—24 6	29	—0 1	+0 4	+65
Victor J 4/10/13	24	Falling temperature immediately after chill	40 5-39 2		0 77	1 9	62 1	—7 0		—1 3	—0 8	+81
Sam F 4/12/17	32	Falling temperature, profuse sweating	39 1 38 7	84	0 79	1 6	55 5	—7 0	36	—0 4	—0 3	+40
Paul K 3/17/17	30	Late falling temperature	38 5 37 9	80	0 79	1 4	48 5	+0 5	34	—0 6	—1 1	—23

* Meeh's formula

TABLE 2-A—Calorimetry Data After Food

Name and Date	Body Weight, Kg	Food: Total Calories	Food: Carbohydrate, Gm	Food: Fat, Gm	Food: Nitrogen, Gm	Urine N	Feces N, Estimated	Excreta N	Nitrogen Balance	Urine Volume, C c	Length of Period, 24 Hours
George S March 14		1,089	85.5	63.9	5.6	11.2	1.1	12.3	—6.2	865	19 hours 2 minutes
March 15		2,690	278.0	130.0	13.4	17.8	1.3	19.1	—5.7	1,070	23 hours 45 minutes
March 16	.	2,900	323.0	128.0	14.9	14.1	1.5	15.6	—0.7	1,070	24 hours 15 minutes
March 17	70.4	3,000	310.0	131.0	15.0	15.3	1.5	16.8	—1.8	1,340	23 hours 45 minutes
March 18	69.8	2,950	308.0	140.0	15.1	13.5	1.5	15.0	—0.1	1,190	
March 19	.	3,300	384.0	144.0	15.1	14.4	1.5	15.9	—0.8	1,080	
Paul K March 16	57.4	1,750	171.0	86.0	9.6	19.4	1.0	20.4	—10.8	1,130	
Fred E March 18	56.9	2,470	248.0	115.0	15.0	13.2	1.5	14.7	+0.3	890	
March 19	56.5	2,500	238.0	114.0	15.1	12.1	1.5	13.6	+1.5	1,030	
Sam F April 11	59.5	1,230	119.0	57.0	8.2	12.2		13.0	—4.8	580	
April 12	60.6	1,790	178.0	83.0	11.3	14.8	1.18	15.9	—4.6	865	
April 13	60.5	1,885	180.0	97.0	9.6	13.0	1.0	14.0	—4.4	1,180	
April 14		2,470	210.0	119.0	14.9	14.6	1.5	16.1	—1.2	1,610	
April 15	60.9	2,415	242.0	112.0	14.7	16.2	1.5	17.7	—3.0	1,510	
April 16	60.7	2,510	211.0	123.0	15.1	12.5	1.5	14.0	+1.1	1,020	
April 17		2,530	249.0	122.0	14.7	12.5	1.5	14.0	+0.7	1,340	
April 18	60.6	2,450	240.0	117.0	14.8	11.4	1.5	12.9	+1.9	1,100	

Case 4—Fred E , tertian malaria

History—A farmer's helper, born in the United States, 18 years of age He was admitted March 16, 1917, and discharged improved March 28, 1917 While in Mexico in 1912 he contracted malaria and has had recurrences every spring lasting from two to four weeks During the first three attacks the chills occurred every second day For the past two years, however, he has had a chill every morning during the attacks

March 13, three days prior to admission, he was seized with a chill followed by high fever which lasted two to three hours A similar paroxysm occurred on the two following mornings He had a very severe headache and a frequent, painful cough During the morning of the admission day he had a severe chill

Physical Examination—A short, moderately well nourished boy He is pallid and his face is covered with pimples The tongue shows a slight white coat The tonsils are moderately enlarged There is no general lymphatic enlargement Heart The left border of dulness, in the fifth space, is 13 5 cm from the median line, the right border is in the fourth space 4 cm from the median line A harsh systolic murmur is heard in the third and fourth spaces half way between the median line and the left border The spleen is very much enlarged downward and toward the median line, 10 cm below the costal margin in the left midclavicular line

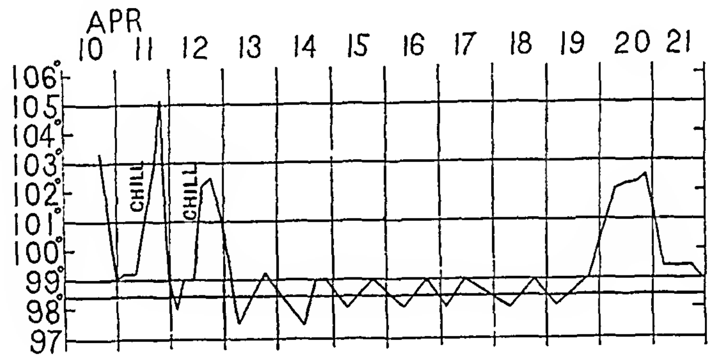

Fig 5—Temperature chart of Sam F

His urine was negative March 17, erythrocytes were 3,912,000, leukocytes 4,200, polymorphonuclears, 71 per cent , lymphocytes, 17 per cent , large mononuclears, 7 per cent, and malarial parasites of tertian form were found

At the time of admission, the afternoon of March 16, the temperature was still elevated (101 8 F) from the chill of the morning It reached normal the following morning and remained so until the time of discharge March 23 he was observed in the calorimeter for three hours He was given quinin for the first time March 25, and March 28 was sent to a convalescent home

Case 5—Sam F , tertian malaria

History—A seaman, born in Sweden, 32 years of age He was admitted April 9, 1917, to the service of Dr Alexander Lambert at Bellevue Hospital, transferred to the metabolism ward April 10 and discharged cured April 30, 1917 He had gonorrhea with epididymitis nine years prior to admission At the same time he had soft chancres with resulting bubo which, however, did not suppurate He denies syphilis He drinks three or four glasses of beer a day, no whisky

In August or September, 1916, while in Java, he developed malaria He had chills every second day during the trip from Java to Genoa, Italy On his arrival in Genoa he went to a hospital where he was treated until March 4, 1917 During most of the time he had no chills He continued treatment until

March 20 He arrived in this country March 27 and had the first recurrence of chills April 9, the day of admission to Bellevue Hospital

Physical Examination—A fairly well nourished, muscular, young man He has a moderate dorsal kyphosis with right lateral scoliosis The tongue shows a slight white coat The tonsils are large The spleen is felt three finger breadths below the costal margin The edge is hard, firm and rather thick On the skin of the prepuce there are two small, nonindurated ulcers, probably due to filth

Urine Negative, except for a few pus cells Blood April 9, 1917, erythrocytes, 4,600,000, hemoglobin, 90 per cent (Sahli), leukocytes, 4,600, Wassermann, negative Gonococcus fixation test, negative

He had a severe chill April 10 and another April 11, during which he was observed in the calorimeter April 12, at 1 50 p m, he had a chill lasting forty minutes He was in the calorimeter from 3 to 5 p m April 13 he did not have a chill although no quinin had yet been given He was observed in the calorimeter during the time of the expected chill, 11 a m to 3 p m On the evening of the same day he received quinin, which was continued until April 26, when he complained of ringing in the ears He was rapidly convalescing when, on the 19th, he developed a rather severe tonsillitis From this he recovered rapidly and was discharged as cured on April 30

V DISCUSSION OF EXPERIMENTS

(*a*) *Basal Metabolism in Afebrile Periods*—In all, seven observations were made on the patients when they were without fever Four of these were in the intervals between the paroxysms, three after treatment

TABLE 3—OBSERVATION DURING AFEBRILE PERIODS

Name and Age	Period of Disease	Calories per Sq M per Hour	Surface Area Formula	Per Cent Deviation from Average Normal
Paul K	Between paroxysms	48 5	Lin	+22
George S	1 hour before severe chill	46 8	Lin	+14
Sam F	1 hour before severe chill	44 6	Lin	+12
Sam F	2½ hours before expected chill	44 0	Lin	+ 9
Average				+14
Sam F	After treatment	39 7	Lin	± 0
Fred E	After treatment	42 3	Lin	± 0
Victor J	After treatment	38 9	Mech	+14
Paul K	After treatment	47 4	Lin	+10

Paul K was never seen to shiver while in the hospital As is shown by the temperature chart, however, he had unusual periodic rises in temperature The observation was made twenty-eight hours after the temperature induced by the last paroxysm had reached normal The very marked increase in metabolism in this case may have been due in part to the very profound secondary anemia His erythrocytes were 2,200,000, with a hemoglobin of 30 per cent

Two observations were made on Sam F when afebrile and before treatment The first, April 11, was made during the hour preceding a severe chill The second observation, April 13, was made during the two and a half hours

preceding an expected chill The observation of that day lasted five hours and was continued through the time of the expected chill During the last two hours, however, there were chilly sensations, with a slight rise in temperature Only the first two and a half hours, therefore, were considered as basal Seventeen days after the last paroxysm, four days after the end of vigorous quinin treatment, he was again observed and was found to have a normal heat production

Fred E, who had suffered with annual attacks of malaria for five years, who had a large, firm spleen and a moderate secondary anemia, was examined seven days after the last chill It was suspected that, since there was an increased metabolism between chills, there might be a similar increase in the condition of malarial cachexia No change in metabolism was found, the figure, 42 3 calories per square meter per hour, being normal for a boy of 19

The observation on Victor J was made seven days after the last chill Only the first two hours of the four-hour observation are included in the basal average During the last two hours the patient was very restless There is some doubt as to whether the first portion can be considered as basal because of possible restlessness of the patient Since this experiment was made before the linear formula was devised, the results are expressed in terms of Meeh's formula and compared with 34 2 calories per square meter of surface per hour, the average normal for this formula

From a consideration of the above experiments it is seen that the total metabolism was raised 14 per cent in the afebrile period between chills If the results on Paul K were to be excluded on account of the complicating factor of anemia, the figures would still be 12 per cent above the average basal level Since there was no fever, this increase must be attributed to the nature of the disease itself

Two of the observations on patients after treatment showed a normal metabolism The third case, Victor J, showed an increase of 14 per cent As there are no detailed notes on this observation, and as he was somewhat restless, this can scarcely be included in the basal average

(*b*) *Metabolism During Paroxysms* —In considering the calorimetric aspects of a malarial paroxysm it is well to subdivide it into six phases

1 A basal period for an hour or so before the chill

2 A short period of rising temperature immediately before the chill which might be called the *prodromal phase*

3 The period of the chill itself

4 A period of rising temperature following the chill

5 The period of high, continuous temperature, which corresponds to the clinical stage of heat

6 The period of falling temperature, which might be still further subdivided into the early and late fall of temperature

Six observations were made on the different phases of temperature during the malarial paroxysm one on the rising temperature before, during and after the chill, including one hour of high, continuous temperature, one on the chill and the period immediately preceding, two on the early fall in temperature, and one on a later fall when the temperature was nearly normal A single experiment was made on the

continuous temperature which persisted after the end of the last paroxysm on Paul K

In considering these experiments four main questions of the mechanism of the rise and fall of body temperature will be investigated and discussed

1 The relation of heat production to heat elimination in the rise and fall of temperature

2 The divergence of the direct heat production as indicated by the measurement of rectal temperature from that determined by the method of indirect calorimetry

3 The varying relation during the different phases of temperature of the heat lost in the vaporization of water to the heat production, on the one hand, and the heat elimination on the other

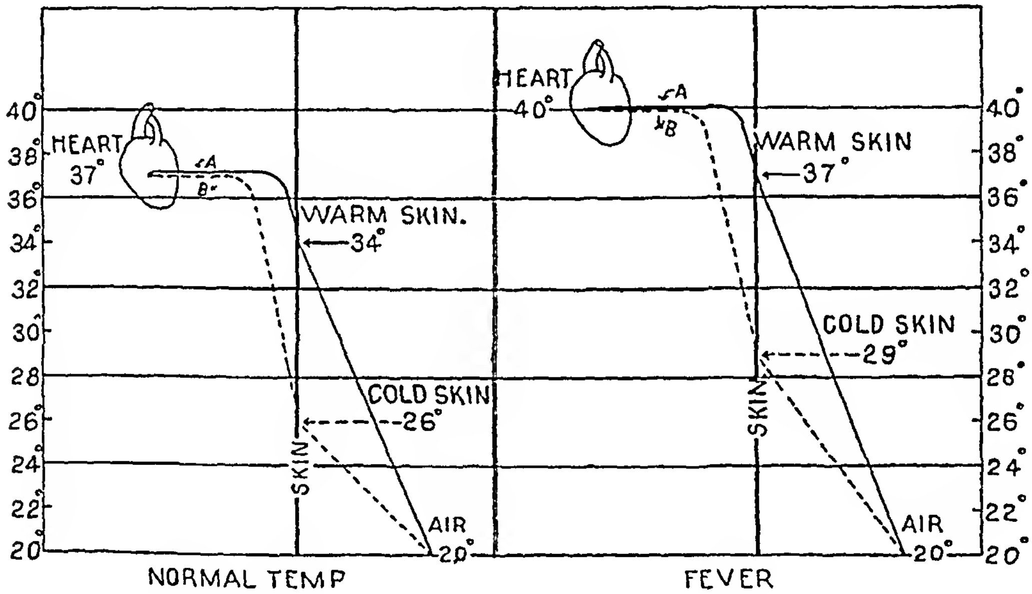

Fig 6—Scheme of body heat loss at different levels of temperature

4 The influence of body temperature on the heat production

The respiratory quotients will be mentioned as indicative of the foodstuffs burned in the different phases of fever

(c) *Heat Elimination in Fever*—In considering the question of heat elimination two questions naturally present themselves First, how is it possible that two individuals of the same size can eliminate the same amount of heat if one has a cool skin and the other a warm skin? Second, how can one explain the fact that the heat elimination of a malarial patient remains almost exactly the same per hour during the period before the chill, during the period of the chill, and during the period of high, continuous temperature immediately after the chill?

The phenomena can be explained with the aid of the diagrams (Fig 6) It is obvious that if the temperature of the interior of the

body, as represented by the heart or the deep rectal region, be 37 C and the outside air be 20 C, there must be a sharp drop somewhere between these two points This can be represented schematically in curves which give the temperature gradients under varying conditions Of course, the temperatures and distances from the skin selected for the charts are not exact, since no actual measurements have been made in these cases

Let us consider the diagram at the left, Figure 6, which shows the gradients that would be found in an individual with a rectal temperature of 37 C exposed to an atmosphere at 20 C Curve A represents the conditions when his skin is warm with, say, a skin temperature of 34 C The interior of the body, up to a point within 1 or 2 cm of the skin, has a fairly uniform temperature and the blood is cooled, either in the skin itself, or perhaps, a centimeter beneath the skin, in other words, the sharp knuckle of the curve representing the sudden fall in temperature lies just beneath the skin The dotted line B represents the same individual with the same rectal temperature exposed to an environmental air of 20 C In this second case, however, the skin is cold, say the surface temperature is 26 C The greatest cooling of the blood takes place at a considerable depth beneath the skin, perhaps 2 or 3 cm In both cases the curves start and end at the same point In both cases the individual produces within his body the same amount of heat per hour and eliminates the same amount of heat per unit of surface In the first instance the cooling is near the surface, and in the second it is deep beneath the skin In the first instance the subcutaneous arterioles are dilated and the warm blood comes in contact with the cooler air In the second instance the surface arterioles are contracted, the subcutaneous tissues are cold, and these cold subcutaneous tissues cool off the blood circulating freely in the deeper structures

In fever or with a changing temperature the phenomena are similar If the internal temperature, for instance, be 40 C, the skin temperature will probably be correspondingly higher The curves representing conditions with warm skin and cold skin start and end at the same points, but the knuckles in the curves representing the sudden drops in temperature are similar to the knuckles in Figure 6

This brings us to a discussion of the average body temperature, a matter of great theoretical interest Probably the average body tempeature will never be determined exactly except under very unusual conditions Some very interesting studies on this subject have been made by Benedict and Slack,[12] working on man, and Henriques,[13]

12 Benedict, F .G, and Slack, Edgar P A Comparative Study of Temperature Fluctuations in Different Parts of the Human Body, Pub 155, Carnegie Institution of Washington, 1911

13 Henriques, V, and Hanson, C Skand Arch f Physiol, 1901, **11,** 161

working on pigs These observers found that the temperature of the interior of the body was fairly uniform until a point was reached 4 or 5 cm from the surface Then there was a gradual cooling until just beneath the surface, where the temperature was several degrees lower than in the interior Other observers have found, also, that some of the internal organs have temperatures averaging higher than others While the temperature taken deep in the rectum is, perhaps, the best single spot to use for the estimation of the body temperature, it is obvious that the actual rectal temperature is higher than that of the whole body, since a large portion of the body lies close to the surface If, for instance, a man weighed 70 kg, there might be as much as 15 kg of tissue within 1 cm of the surface, and the temperature of this surface tissue might, on the average, be 2 degrees cooler than the interior of the body It is obvious no exact calculations can be made For the purpose of drawing curves, however, we can arbitrarily consider that the average body temperature is half a degree below that of the rectum If the skin and subcutaneous tissue should grow colder the average body temperature would be even farther than this below the rectal temperature

While it is impossible to determine the absolute average body temperature, we can calculate the changes in the average body temperature by using a new method This is made possible by the great accuracy of the modern respiration calorimeter We know that in a long series of experiments the methods of direct and indirect calorimetry agree very closely Experiments have shown that the method of indirect calorimetry is accurate within any comparatively short period, and by this method we can find the heat produced within the body during the experimental period Alcohol checks and electric checks have shown that the measurement of the heat eliminated from the body is determined accurately by the calorimeter If, therefore, in any given period we can determine the calories produced in the body and the calories eliminated from the body, the difference between these two represents the calories either stored in the body or lost from its mass of tissue If we know the weight of the body we can calculate its hydrothermal equivalent by multiplying the kilograms by the average specific heat of the body This has usually been assumed to be 0 83, although, as we have pointed out before, the figures may be somewhat lower, especially in obese individuals[14] For our purposes the figure 0 83 is close enough to enable us to determine with a fair degree of accuracy the heat equivalent of the body in

14 See Gephart, F C, and Du Bois, E F Clinical Calorimetry, Paper 4, The Determination of the Basal Metabolism of Normal Men and the Effect of Food, The Archives Int Med, 1915, **15**, 835

terms of kilograms of distilled water If we know the calories stored in the body during a given period and the hydrothermal equivalent of the body, we can easily determine the rise or fall in the average body temperature during a given period If, for instance, during a certain period of the experiment, the heat production, as measured by indirect calorimetry, should be 100 calories and the heat elimination 60 calories, this would mean a storage of 40 calories within the tissues If the body weight were 70 kg, this figure multiplied by the factor 0 83, which represents the specific heat of the body, would indicate that the body, from a thermal standpoint, was equivalent to 58 1 kg of distilled water If 58 1 calories had been stored in the body, the average temperature would have risen 1 degree C, but since only 40 calories were stored in the body, it is obvious that the average temperature rose approximately 0 66 degree C In a similar fashion, if the heat elimination exceeds the heat production, it is obvious that

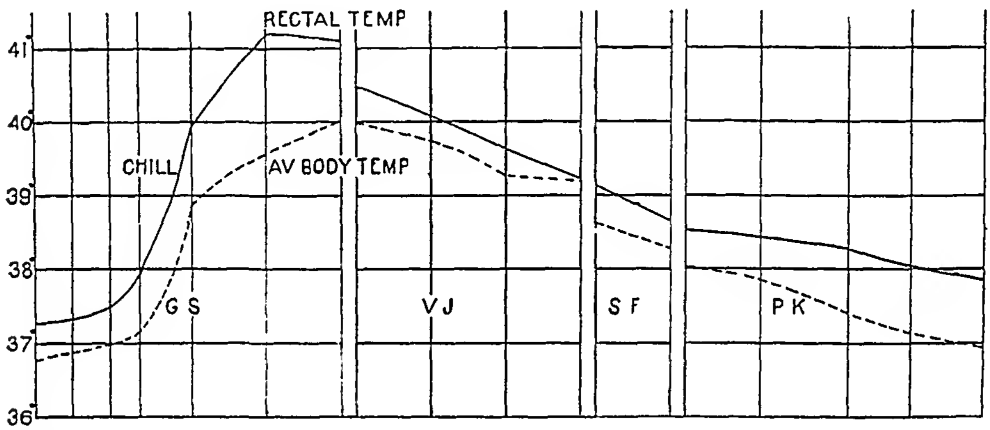

Fig 7—Comparison of changes in rectal temperature and average body temperature Curves constructed from experiments on four subjects in different stages of the malarial paroxysm The continuous line shows the rectal temperature, the dash line indicates the changes in the average body temperature which, for purposes of calculation, is assumed to be one half a degree lower than the rectal temperature at the start of each observation

the average body temperature must be falling This calculation has been made in all the experiments We know the rectal temperature at the start of the experiment and, for the purposes of calculation, the average of body temperature has been assumed to be a half a degree lower If, for instance, in the above period the rectal temperature at the start had been 37 0 C, we would assume that the average body temperature was 36 50 C At the end of the period the average body temperature would have been 37 16 C Perhaps the rectal reading at this same time might have been 38 1 In a similar fashion the change in the average body temperature in the next period would have been calculated, using as a starting point the figure 37 16

This is a roundabout method of calculating temperature changes, but it is believed to be more accurate than any system which depends on a single thermometer in a place like the rectum, where it can be moved from side to side or can be embedded in feces, or in a place like the axilla, groin or mouth, where the thermometer may be affected by a partial opening of the cavities

In the following discussion we shall compare the average body temperature as obtained by this method with the rectal temperature In this way we can obtain some idea of the accuracy of rectal temperature as an index of the temperature of the body during a paroxysm

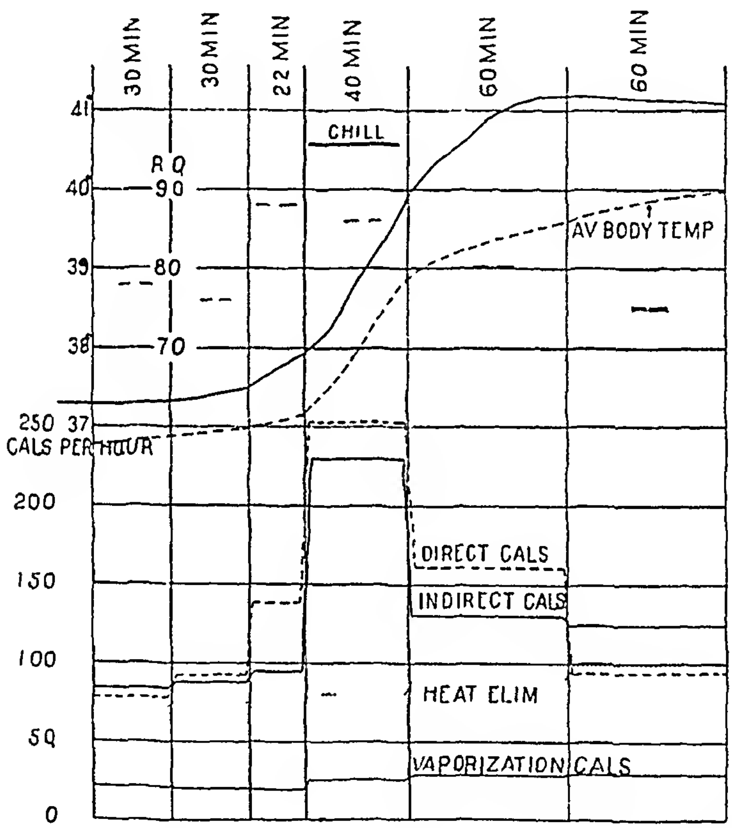

Fig 8—Metabolism chart of George S, March 14, 1917

(*d*) *Individual Experiments During Paroxysms*—

George S, March 14, 1917, Chart 8 The curves show the relationship of heat production and heat elimination before, during and after a malarial chill The uppermost line shows the changes in rectal temperature The accompanying dash line shows the changes in the average body temperature The middle dash line represents the heat production in calories as measured by the direct method, the solid line, the heat production by the indirect method, the dotted line, the heat eliminated, and the lowest solid line, the calories lost in the vaporization of water The respiratory quotients are represented above the rectal temperature by dashes for each period

Phase I—Normal temperature (Periods 1 and 2) The metabolism is 14 per cent above the average basal level for a boy of 19 The direct and indirect calories agree exactly The rectal temperature indicates a rise of 0 2 degree C,

which corresponds exactly to the increase in average body temperature The total heat elimination is at a level slightly below the heat production The heat lost in vaporization is 29 per cent of the total heat eliminated, 26 per cent of the heat produced (direct method) The respiratory quotient is normal

Phase II—Rising temperature before chill (Period 3) Heat production is 21 per cent above basal level The direct method indicates a higher metabolism The rectal temperature shows a rise of 0 44 degree C The average body temperature rises only 0 15 degree C Heat elimination does not change from its former level The heat lost in vaporization of water is 28 per cent of the total heat elimination, only 14 per cent of the direct heat produced The respiratory quotient rises to 88

Phase III—Violent chill (forty minutes) (Period 4) Heat production is 216 per cent above the average normal level The heat production as measured by the direct method is higher than is indicated by the indirect The rectal tem-

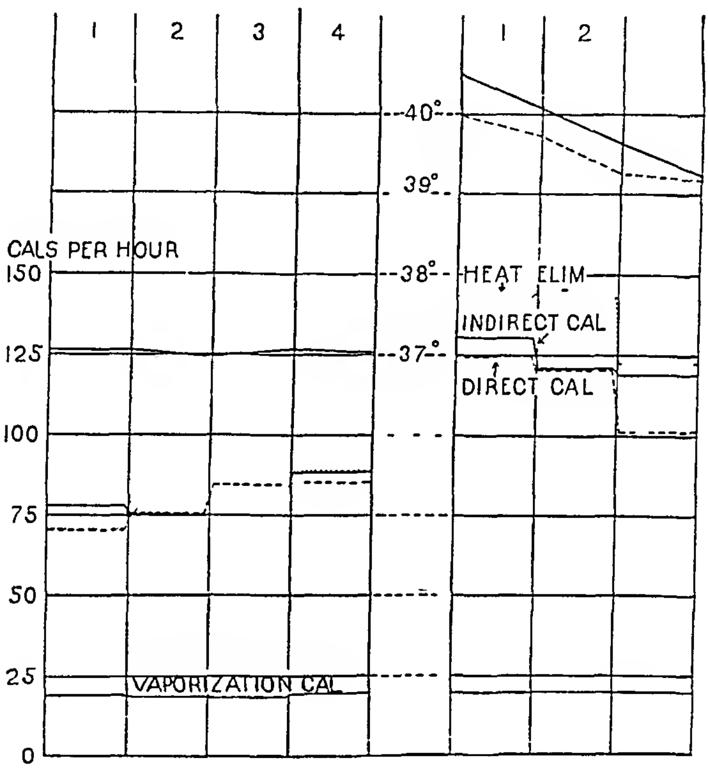

Fig 9—Metabolism chart of Victor J, April 10 and April 16, 1913

perature shows a rise of 2 0 degrees C, the average body temperature 1 7 degrees C The total heat elimination is raised very slightly The heat lost in vaporization of water is 31 per cent of the total heat eliminated, only 10 per cent of the heat produced (direct method) The respiratory quotient is high, 0 86

Phase IV—Rising temperature following chill (Period 5) Heat production drops to 80 per cent above the normal basal level The heat production, as measured by the direct method, is higher than is indicated by the indirect The rectal temperature shows a rise of 1 3 degrees C, the average body temperature only 0 7 degree C The total heat elimination has risen to a higher level The heat lost in the vaporization of water is 31 per cent of the total elimination, 18 per cent of the heat produced (direct method) The respiratory quotient is 0 80

Phase V—High, continuous temperature (Period 6) Heat production is 71 per cent above the normal basal level The heat production as measured by the direct method is not so high as is indicated by the indirect method The rectal

temperature shows a fall of 0 1 degree C, the average body temperature a rise of 0 4 degree C The total heat eliminated has again risen and is now higher than the heat produced as measured by the direct method Heat lost in vaporization is 29 per cent of the total heat eliminated, 31 per cent of the heat produced (direct method) The respiratory quotient is 0 76

Victor J, April 10, 1913, Chart 9 The curve in Figure 9 shows the relationship between heat production and heat elimination during early fall in temperature The lines correspond to those on Chart 8 The left hand portion of the chart shows the results obtained on a day without fever On right is the observation of three hours in length, immediately after the chill Heat production is 81 per cent above the average basal for a male adult The heat production as measured by the direct is not so high as is indicated by the indirect The rectal temperature indicates a drop of 1 1 degrees C, the average body temperature only 0 8 degree C The total heat eliminated is higher than the heat produced The percentage of heat lost by vaporization is not accurately measured At the time of the observation (1913) ventilation was not sufficient to remove the water Respiratory quotients average 0 76

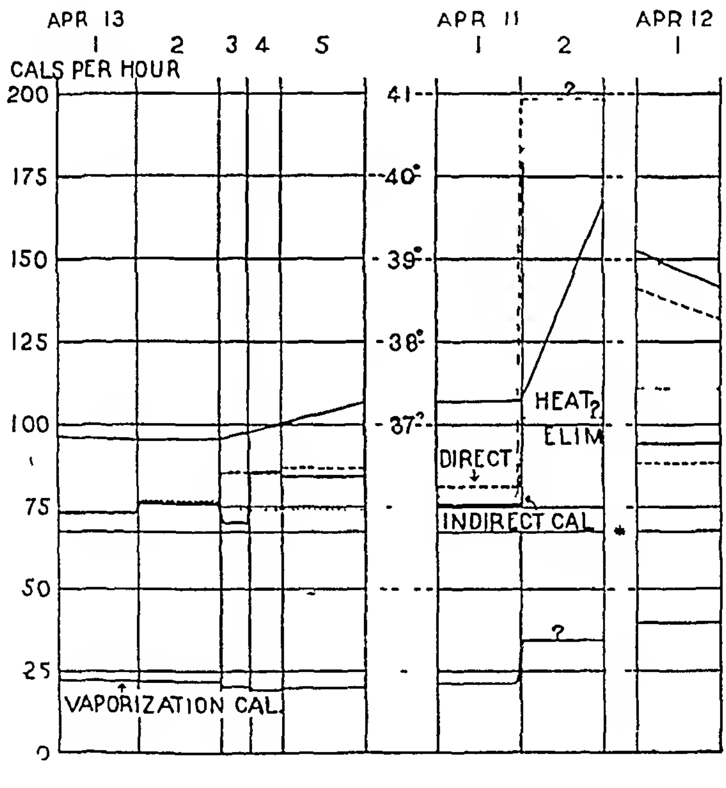

Fig 10—Metabolism chart of Sam F, April 10, 11, 12, 1917

Sam F The curves in Figure 10 show the relationship of heat production and heat elimination before, during and after chill The lines correspond to those on Figure 8 The chart includes three observations made on April 11, 12 and 13, 1917

Phase I—Normal temperature before expected chill (Periods 1 and 2) Heat production is 11 per cent above the average basal level Direct and indirect methods agree Both rectal and average body temperature remain constant Total heat elimination corresponds to heat production The respiratory quotient is 0 78

Phase II—Rise in temperature before expected chill (Period 3) Heat production by the indirect method 3 per cent above the average basal level Heat production by the direct method rose slightly Average body temperature

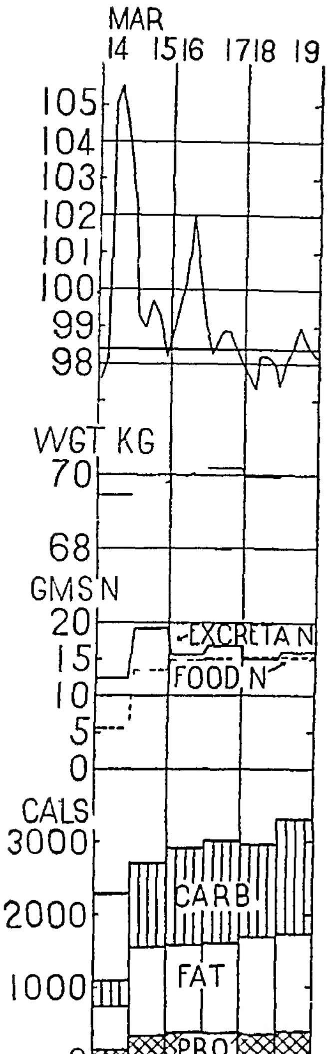

Figure 11

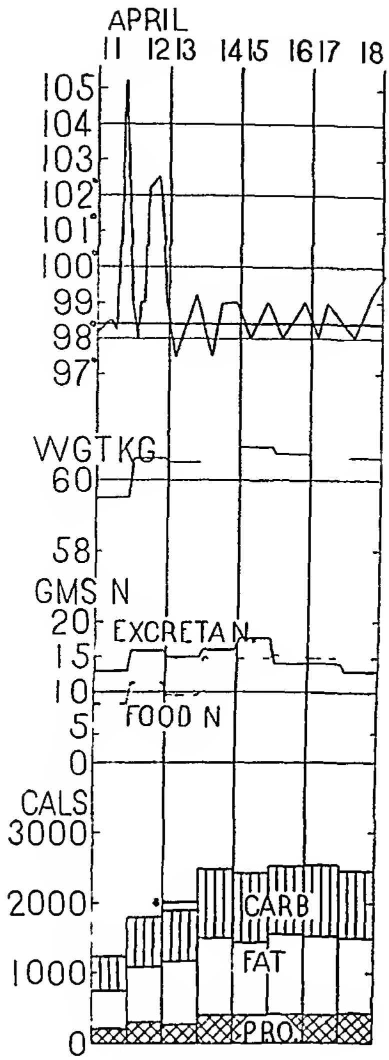

Figure 12

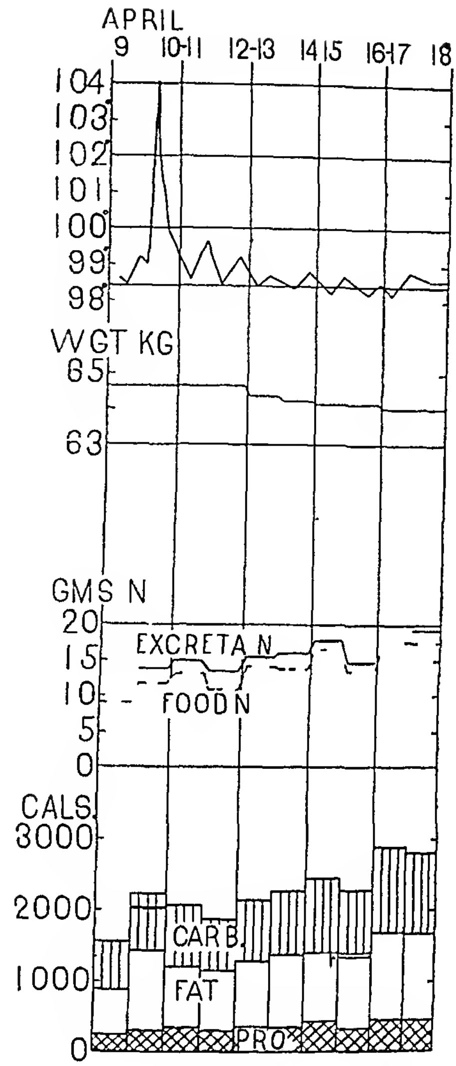

Figure 13

Fig 11—George S Temperature, weight, nitrogen balance and food chart
* Small dot and heavy horizontal line at level of about 2,200 calories show estimated heat production for twenty-four hours

Fig 12—Sam F Temperature, weight, nitrogen balance and food chart
* Small dot and heavy horizontal line at level of about 2,000 calories show estimated heat production for twenty-four hours

Fig 13—Victor J Temperature, weight, nitrogen balance and food chart
* Small dots and heavy horizontal lines at level of about 2,000 calories April 10, and at about 1,200 calories April 16, show estimated heat production for twenty-four hours

dropped slightly, rectal temperature rose 0 1 degree C Heat elimination did not change its level The respiratory quotient was unchanged

Phase III—Chilly sensations, no chill (Periods 3 and 4) Heat production 27 per cent above the average basal level The direct and indirect methods agree The rectal temperature shows a rise of 0 3 degree C The average body temperature shows a corresponding rise Heat elimination does not rise with production but remains at its former level

Observation made on April 11, 1917 Phase I (Period 1) —Normal temperature preceding severe chill Heat production is 12 per cent above the average

basal level Indirect calorimetry not entirely reliable because of a slight amount of oxygen admitted from the preliminary period Heat elimination at corresponding level

Phase III—Severe chill The results were ruined by an accident caused by enormous increase in metabolism (sulphuric acid bubbled into the sodium bicarbonate can, generating carbon dioxid, water and heat) The period is included to show the large amount of heat stored in the body during the chill

Observation made April 12, 1917 Falling temperature with sweating Heat production is 40 per cent above the basal level Heat elimination is tremendously increased Heat production by the direct method is lower than is indicated by the indirect Rectal temperature fell 0 46 degree C, average body temperature fell 0 33 degree C The heat lost in vaporization was 36 per cent of the total heat elimination This did not include all of the water eliminated for the humidity in the calorimeter began to rise during the last ten minutes of the period

Paul K, March 17, 1917 Late falling temperature Heat production was 22 per cent above the normal level The production by the direct method was higher than was indicated by the indirect Rectal temperature fell 0 7 degree C during the observation Average body temperature fell 1 1 degrees C Heat elimination was much higher than heat production Heat lost in vaporization was 27 per cent of the total heat eliminated, 26 per cent of the heat produced (direct method) during the first hour At the end of the first hour the patient spilled the urine, thus spoiling the results of water vaporization The respiratory quotients were about 0 79

Another observation was made on Paul K March 20, after the end of the last paroxysm, when his temperature was still elevated On this day his heat production was + 19 per cent, slightly lower than it had been four days before in the afebrile period between paroxysms

(*e*) *Nitrogen Balances*—In Figures 11, 12 and 13 will be found graphic representations of the food administered, temperature curve, weight curves and the relationship between food nitrogen and excreta nitrogen

In the case of George S it will be seen that there was a negative nitrogen balance during the febrile period in spite of an intake of 3,000 calories a day The patient came to a nitrogen equilibrium when the malarial paroxysms ceased

In the case of Sam F the nitrogen balance remained negative until the fourth day of normal temperature, although his food intake had reached about 2,400 calories on the second day of normal temperature

Victor J showed a negative nitrogen balance six days after his last paroxysm, but his intake was little over 2,000 calories

In general, it will be noted that malarial patients gave evidence of a toxic destruction of protein, just as did the typhoid patients studied in Paper 7 of this series[15] In spite of caloric intake, which covered the heat production and supplied an ample amount of protein and carbohydrate, there was a negative nitrogen balance

(*f*) *Direct and Indirect Calorimetry* —In the observations on malarial patients without temperature, the heat production, as mea-

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15 Coleman, W, and Du Bois, E F Clinical Calorimetry, Paper 7, Calorimetric Observations on the Metabolism of Typhoid Patients With and Without Food, The Archives Int Med, 1915, **15**, 887

sured by the direct method, amounted to 917 1 calories, by the indirect, to 927 1 calories, a total divergence of —1 1 per cent In the observations in fever the total heat production by the direct method was 1,675 7 calories, by the indirect, 1,664 1 calories, a divergence of +0 7 per cent In the febrile experiments the variations for the individual hours was often very great In the period for the chill on George S the direct calorimetry showed a heat production of 49 per cent above that shown by the indirect The greatest divergence for any single observation was 7 per cent Six of the eleven experiments showed a divergence of 5 per cent or less The total heat production for all observations was 2,592 8 calories, as measured by the direct, and 2,591 2 as measured by the indirect, a total divergence of + 0 08 per cent

TABLE 4—Percentage Divergence of Direct from Indirect Calorimetry in the Individual Experiments

Percentage Divergence	Number of Experiments Falling in Each Group		
	Plus Divergence	Minus Divergence	Total
0 - 5	2	4	6
5 - 7	2	3	5
	Indirect	Direct	Divergence, per Cent
Afebrile Experiments	927 1	917 1	—1 1
Febrile experiments	1,664 1	1,675 7	+0 7
Total calories measured in all experiments	2,591 2	2,592 8	+0 08

(*g*) *Character of Foodstuffs Burned*—All of the respiratory quotients were within normal limits, the highest being 0 88, the lowest 0 72 Before and during the chill on George S the quotients were higher than in any of the other periods This shows an increased combustion of carbohydrate and would indicate a mobilization of the glycogen stores of the body It is particularly interesting that the quotient rose before the chill and even before there was any noticeable increase in metabolism As this period was only twenty-two minutes in length, it is unsafe to draw from it any conclusions

The close agreement between the direct and indirect methods during the observations, the consistently normal respiratory quotients, indicate that there is no change in the metabolism of malaria sufficiently profound to upset calculations based on the method of indirect calorimetry

(*h*) *Relation of Heat Production to Heat Elimination*—From a consideration of the preceding experiments one relation stands forth with distinctness The comparison of heat elimination and heat production shows unmistakably that the rise in temperature is chiefly dependent on an increase in heat production and that the heat elimination does not change The temperature is maintained at a high level by a heat production which is still high, and an elimination which, although rising, is not adequate to take care of the heat produced The fall in temperature is accomplished by a combination of two factors, a decrease in heat production and an increase in heat elimination Of the two factors, however, the increase in elimination is much more striking

(*i*) *Periods of Malarial Paroxysms*—A malarial paroxysm has usually been divided into three stages first, that of heat, second, that of fever, third, that of sweating On closer analysis this rough clinical division is not satisfactory for a description of the changes in heat regulation The following subdivision into six stages gives one a better chance to describe the phenomena observed in the calorimeter experiments

1 *Preliminary Period* The rectal temperature remains constant and there is no warning of the coming paroxysm

2 *Prodromal Period* Fifteen or twenty minutes before the chill the rectal temperature begins to rise a little The patient begins to feel a little uncomfortable

3 *Period of Chill* This may last a few minutes or as long as an hour The rectal temperature rises abruptly The surface of the body may become relatively and perhaps actually cooler The average body temperature, therefore, rises somewhat less abruptly than the rectal temperature The patient feels cold and shivers violently

4 *Period of Rising Temperature After the Chill* The rectal temperature rises less rapidly than during the chill The surface of the body becomes warmer The patient feels weak and exhausted after his chill

5 *The Period of High, Continuous Temperature* The rectal temperature changes but little The surface temperature rises steadily The patient feels hot

6 *Period of Falling Temperature* The rectal temperature falls much more gradually than it rose During the very earliest stage of this period the surface temperature is still rising Soon it begins to fall, but not so rapidly as the internal temperature In the latter part of the period the two fall at about the same rate The patient sweats profusely

Heat Production In the preliminary period this is unchanged In the short prodromal period there may be an insignificant rise During the chill the violent muscular exercise increases heat production 100 to 200 per cent [16] Immediately after the chill there is a marked decrease in the heat production which falls to within 20 to 38 per cent of the average basal level During the remaining periods it decreases slowly until it reaches the normal

Heat Elimination During the preliminary period the heat elimination, of course, equals heat production During the prodromal period before the chill it shows little or no change During the chill the heat elimination remains almost exactly the same as during the preliminary period In spite of the enormous increase in heat production the amount of heat which leaves the surface of the body is almost exactly the same as before the chill The blanching and coldness of the surface have not decreased the actual amount of heat eliminated In the fourth period, of rising temperature after the chill, there is slight increase in the heat elimination, but, of course, the elimination still lags behind the production In the fifth period, of continuous temperature, the heat elimination rises and begins to equal the heat production In the sixth period, of falling temperature, the heat elimination is greatly increased

Vaporization The actual amount of heat lost through the vaporization of water through skin and lungs amounts to about 25 per cent of the total heat *elimination* in the preliminary period This percentage ratio remains fairly constant during all the periods The actual number of calories lost by vaporization per hour changes very little during the first five periods, but rises abruptly during the last period The patient then loses a large amount of heat during the vaporization of sweat

Respiratory Quotient During the prodromal period and chill, as a rule, the respiratory quotient is higher than after the chill, suggesting the rapid combustion of the glycogen stores during the violent muscular exercise

(*j*) *Changes in Rectal Temperature and in Average Body Temperature*—Maragliano,[17] in 1888, working on malaria patients with a Mosso plethysmograph, found that the volume of the arm decreased not only during the chill but before the chill, even before any chilly sensations had been felt When the temperature began to fall the volume of the arm increased to a point far above its original level

16 Lusk, G (Footnote 11) found a maximum increase of 180 per cent in the heat production of a thin man during the violent shivering which followed immersion for nine minutes in water at a temperature of 10 C

17 Maragliano Das Verhalten der Blutgefasse im Fieber und bei Antipyrese, Ztschr f klin Med, 1888, **14**, 309

He concluded from his experiments that before the chill there is a contraction of the superficial blood vessels which precedes rise in temperature, that during the chill the blood vessels are still further contracted, and that they remain in that condition until the temperature begins to drop, when there is a marked dilatation He found, also, that the dilatation of blood vessels precedes by a short interval the drop in temperature, but continues to increase during the rapid fall

It may be that we have here in this curve a confirmation of these findings Just as Maragliano found a contraction in superficial blood vessels before the rise in temperature, so we have found an increase in the temperature of the rectum before the chill From these facts it might be assumed that the blood is driven from the surface to the inside of the body Any extra heat which is produced during this period would, under these conditions, be stored in the interior of the body The rectal temperature would therefore rise

So, also, during the chill and in the hour following it the heat produced is stored more rapidly in the deeper organs of the body than near the surface

When the rectal temperature begins to fall the average body temperature is still rising and probably continues to do so for a considerable period

During the stage of falling temperature the heat which has been stored in the deeper structures is being given off rapidly to the rest of the body The heat elimination has been raised to an abnormal level But, with both radiation and conduction and water elimination increased, the skin and lung surfaces are not able to throw off the heat as rapidly as it is produced anew and delivered from the inside of the body

This condition might be represented by the following simple diagram

Interior of body $\rightrightarrows$ Periphery of body $\rightarrow$ Outside air

The interior of the body is losing heat rapidly to the surface layers of the body, which are in turn losing heat less rapidly to the outside air The mechanism of heat loss in the body has not yet recovered its function sufficiently to eliminate the heat which is already stored in the body as well as that which is being produced at the time

It is interesting and important that, during this obvious attempt on the part of the body to rid itself of heat, there is no marked decrease in heat production To be sure, there is a very gradual lowering of production to the normal level, but there apparently is no mechanism by which the heat production can be lowered abruptly It may be that during the drop in temperature the heat production is proportional to the level of the temperature During the end of the fall the heat pro-

duction is on a much lower level The heat elimination is high The inside of the body loses heat slowly, the periphery eliminates it rapidly The mechanism of loss has by this time apparently recovered its complete function This simply means that the heat which had accumulated at the surface of the body is now being eliminated The inside of the body has lost to the periphery most of the heat which was stored within it during the period of high fever and is now near its normal level

The results on the heat lost in vaporization show two things with distinctness Formerly, the water elimination has been studied chiefly in patients without fever Under these conditions, over any extended period, the heat production, as figured by the method of direct calorimetry, equals the heat elimination Under these circumstances it does not matter whether the heat of vaporization be compared to the heat production or to the heat elimination In fever observations, however, the heat elimination and heat production vary within wide limits Thus, in the observations on malaria, comparison of the heat of vaporization with the heat production gives variations of 10 to 45 per cent On the other hand, the comparison of the heat of vaporization with the heat eliminated shows variations within much narrower limits, 23 to 36 per cent If the observation on the sweating patient, Sam F, be omitted the variation is between 23 and 31 per cent It can therefore be said with some degree of certainty that heat of vaporization is a function of heat elimination and that it has no relationship to the heat produced

In the rapid fall, with sweating, observed on Sam F, the percentage of heat of vaporization to total heat eliminated was even more increased above the usual level than is shown by the figures It is certain in this case that not all of the water was removed by the ventilation of the chamber

VI SUMMARY AND CONCLUSIONS

Eleven calorimeter experiments have been made on patients in different periods of malarial fever, six of them being made during paroxysms In all cases the methods of direct and indirect calorimetry were used For the total series of experiments the calories, as measured by these two independent methods, agree within 0 08 per cent of each other In some of the individual observations the divergence between the two was as great as 7 per cent, in some of the short periods the divergence was much greater

The rectal temperature, which was measured every four minutes, showed typical malarial curves The temperature curve of the deep parts of the body, as represented by the rectal region, does not indicate correctly the changes in the average body temperature In a man

weighing 70 kg about 15 kg of tissue lie within 1 cm of the surface This subcutaneous layer may be warm or cold When it is warm the blood from the interior of the body is cooled at the surface of the skin When the subcutaneous layer is cold the largest mass of blood loses heat 1 to 3 cm below the skin A man producing a constant amount of heat every hour may eliminate from his surface exactly the same amount of heat with warm skin as with cool skin A malarial patient may eliminate exactly the same amount of calories per hour before his chill as he does during the period of high temperature before the sweating begins The changes in the average temperature of the body have been measured by a method based on the difference between the indirect and direct calorimetry during individual periods This new method is possible only with a respiration calorimeter

The periods of malarial paroxysms may be divided as follows

1 *Preliminary* Temperature constant, no change in metabolism

2 *Prodromal* Fifteen or twenty minutes before the chill there is a slight rise in rectal temperature

3 *Chill* Rectal temperature rises abruptly, the surface of the body becomes relatively and perhaps actually cooler, the average body temperature rises somewhat less abruptly than the rectal temperature

4 *Rising Temperature After Chill* Rectal temperature rises less rapidly than during chill, the surface becomes warmer

5 *High, Continuous Temperature* Rectal temperature is constant, surface temperature rises steadily, patient feels hot

6 *Falling Temperature* Rectal temperature falls much more gradually than it rises The surface temperature at first may continue to rise, then to fall gradually for a period, and later to fall at about the same rate as the rectal temperature

The *heat production* increases 100 to 200 per cent during the chill, immediately after the chill it falls to within 20 to 38 per cent of the average basal level, with the falling temperature the heat production drops to normal

During the period before the chill with constant temperature the *heat elimination,* of course, equals the heat production During the chill, in spite of the enormous increase in heat production, the heat elimination is the same as in the preliminary period Almost all of the extra heat produced is stored in the body tissues

In the fourth period of rising temperature after the chill there is a slight increase in heat elimination In the fifth period of continuous temperature heat elimination begins to equal heat production In the sixth period of falling temperature the heat elimination is greatly increased, chiefly by means of a large increase in the vaporization of water from the skin Of the total calories produced in this period the

patient loses a much larger percentage than normal through vaporization On the other hand, the percentage of calories lost through vaporization is not greatly increased in its relationship to the total heat elimination

The respiratory quotients during the chill are higher than before or after the chill, suggesting the rapid combustion of glycogen stores during the violent muscular exercise of shivering

CONCLUSIONS

In malarial paroxysms the increase in body temperature is due to an increasing heat production, which more than offsets a slightly increasing heat elimination

The fall in body temperature is due to a greatly increased heat elimination with a heat production which is very slightly raised above the normal

There is no indication of abnormal processes of metabolism in malarial fever except that the protein metabolism is somewhat increased

In two observations on patients after treatment the basal heat production was normal

During a malarial paroxysm the rectal temperature rises somewhat more rapidly than the average body temperature

Except for the period of chill the level of the heat production is roughly proportional to the height of the body temperature

During a malarial paroxysm the percentage of heat lost in vaporization of water bears a fairly constant relationship to the heat elimination but not to the heat production

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A FURTHER STUDY OF ETHYLHYDROCUPREIN (OPTOCHIN) IN THE TREATMENT OF ACUTE LOBAR PNEUMONIA *

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In a previous communication[1] we reported on a series of thirty-two cases of lobar pneumonia due to pneumococci and treated with ethylhydrocuprein (optochin) hydrochlorid By means of bactericidal tests of the patient's serum in vitro the absorption and elimination of the drug in these cases was studied It was concluded that the hydrochlorid of the drug is rapidly absorbed from the gastro-intestinal tract into the circulating blood, that when an amount of the hydrochlorid represented by 0 024 to 0 026 gm per kilogram of body weight of the patient is administered by mouth per twenty-four hours, the blood serum of the patient acquires the property of destroying pneumococci in the test tube, that the best way to insure the rapid production and maintenance of this bactericidal action in the blood is to divide the total amount of the drug in such a way that the first dose is relatively large and is followed at intervals of not more than three hours by smaller equal doses For example, if the patient is of average size and is to receive 1 5 gm in twenty-four hours, he is given a first dose of 0 45 gm, and this is followed by seven doses of 0 15 gm each at regular intervals It was further shown that during administration of the drug the pneumococci in the body may become "fast" or resistant to a considerable concentration of ethylhydrocuprein

The purpose of the present paper is to present the data accumulated in an extension of the former work and to give the final results of two years' experience in the treatment of lobar pneumonia with ethylhydrocuprein It may be stated that the experimental results obtained during the first year have been for the most part confirmed by the study of cases treated during the second year, and, in addition, some new facts have been ascertained which it is desirable to record The experimental observations will be recorded first, and then the entire series of cases will be analyzed from a clinical standpoint

The method of investigation described in the previous paper has

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1 Moore, H F, and Chesney, A M THE ARCHIVES INT MED, 1917, **19**, 611

again been used and has been found satisfactory Briefly, this consisted in repeated determinations of the bactericidal power of the patient's serum at 37 5 C for young (four to six hours) broth cultures of pneumococci The strains used were stock strains and usually the type of pneumococcus employed for any case differed from that causing the infection Almost all the patients admitted to the wards of the Hospital of The Rockefeller Institute from October, 1915, to May, 1917, suffering from lobar pneumonia due to pneumococci belonging to Groups II, III and IV, were treated with ethylhydrocuprein Cases due to pneumococci of Group I did not receive ethylhydrocuprein, but were treated with specific immune serum A limited number of patients infected with pneumococci of Groups II and III were treated with ethylhydrocuprein by mouth and in addition received type homologous immune serum intravenously, or concentrated "extract" of such serum subcutaneously or intravenously

Of the forty-three patients treated with ethylhydrocuprein during the season 1916-1917, two received the base (optochin base) by mouth Forty received the hydrochlorid by mouth and one patient received the hydrochlorid intramuscularly at first, and later by mouth In Table 8 are presented the details as to dosage of the drug, clinical features and so forth, in these forty-three cases

ADMINISTRATION OF ETHYLHYDROCUPREIN BASE BY MOUTH

The serum of the patients (Nos 2786 and 2783) who received the base by mouth failed to show either bactericidal activity or power temporarily to inhibit the growth of pneumococci, although the amount of the drug given should have been sufficient to produce such a result if the base were as readily absorbable as the hydrochlorid The difficulty of absorption from the gastro-intestinal tract is undoubtedly dependent on the fact that the drug in this form is very slightly soluble

"FASTNESS" OF PNEUMOCOCCI TO ETHYLHYDROCUPREIN

In our former communication we reported one instance in which the infecting pneumococcus became "fast" to ethylhydrocuprein in the human body A further example of this phenomenon has been observed in the present study The details follow

Hosp No 2825—A street cleaner, aged 50, weight 69 kg

Past History—Unimportant

Present Illness—Cough for one day, chill and bloody expectoration on day of admission

Status on Admission—Patient dyspneic, cyanotic and decidedly ill, temperature 105 2 F, pulse 120, respirations 32, dulness with suppression of breath sounds and numerous fine moist râles over left lower lobe Leukocyte count 15,000 Sputum tenacious, hemorrhagic and containing Pneumococcus Type II Blood culture showed Pneumococcus Type II, three colonies per cubic centimeter

Course and Treatment—Ethylhydrocuprein hydrochlorid started by mouth on second day of disease, schedule as follows in periods of twenty-four hours first period, 1 × 0 6 gm + 8 × 0 15 gm (0 026 gm per kilo of body weight per twenty-four hours), second period, 12 × 0 15 gm, third period, 11 × 0 15 gm, last period of eighteen hours, 7 × 0 15 gm + 2 × 0 1 gm Blood culture taken thirty-six hours after the commencement of the ethylhydrocuprein treatment showed twenty-four colonies of pneumococcus Type II per cubic centimeter of blood and the patient's general condition seemed worse at that time On the following day the blood culture showed sixty colonies per cubic centimeter and on the last day of life blood culture showed 700 colonies of Pneumococcus Type II per cubic centimeter of blood The patient became progressively worse and died on the fifth day after admission to the hospital Judging from physical signs, spread of the infected area in the lungs did not take place The total amount of ethylhydrocuprein given was 6 5 gm No toxic symptoms referable to the drug were observed

Samples of blood serum of this case were obtained before beginning treatment and eight times during the course of treatment, these samples were tested for pneumococcidal power against a four-hour-old culture of Pneumococcus Type II Pneumococci grew unhindered in the specimen obtained before beginning treatment, but the tests of the specimens obtained later showed that the ethylhydrocuprein conferred the usual degree of pneumococcidal power on the serum as early as 5 5 hours after the first dose was administered and that this pneumococcidal power was maintained throughout the treatment

The specimens of patient's serum showing pneumococcidal power were pooled and the effect of the pooled serum on two strains of pneumococci, obtained from the patient's blood, was studied, one of these strains was obtained from the patient's blood on admission to the hospital and before the ethylhydrocuprein treatment was started and the other strain from his blood two hours before death The results are given in Table 1 The technic employed was that previously described,[1] using 0 001 c c of a four-hour-old broth culture to inoculate 3 c c of serum The serum was previously heated at 56 C for one half hour The bacterial count of the plates is given in approximate figures

TABLE 1—Results of Ethylhydrocuprein Injections in Hospital No 2825

Serum	Strains of Pneumococcus Obtained from Blood	Number of Colonies of Pneumococci per 0 5 C c of Serum When Plated*		
		Immediately	After 1½ Hours Incubation	After 24 Hours Incubation
Before ethylhydrocuprein was started	On admission (before ethylhydrocuprein)	400	2,000	Confluent
	Two hours before death	400	2,000	Confluent
Pooled specimens obtained during ethylhydrocuprein treatment	On admission (before ethylhydrocuprein)	400	300	0
	Two hours before death	400	2,000	Confluent

* Approximate counts

From Table 1 it is seen that whereas the strain obtained from the patient's blood before the ethylhydrocuprein treatment was started was readily killed by the pooled serum obtained during the administration of the drug, the strain obtained from the blood towards the end

of the treatment and shortly before the death of the patient was completely insusceptible to any pneumococcidal action of the same serum

The effect of various concentrations of ethylhydrocuprein hydrochlorid in broth on the growth of the different strains of pneumococci obtained from this patient was also studied In each test 0 1 c c of an eighteen-hour broth culture of the given strain was inoculated into 5 c c of the broth containing the ethylhydrocuprein, mixed and incubated for forty-eight hours The degree of growth, if any, was judged macroscopically Plates were also poured and smears examined after incubation

TABLE 2—Growth in Broth Containing Various Dilutions of Ethylhydrocuprein Hydrochlorid of Strains of Pneumococcus Isolated from Blood of Hospital No 2825

Designation of Strain	Isolated	Number of Colonies in 0 000001 C c of Culture Used in Tests
A	From blood on admission	85
B	From blood on second day of ethylhydrocuprein treatment	101
C	From blood on third day of ethylhydrocuprein treatment	162
D	From blood on fourth day of ethylhydrocuprein treatment (2 hrs before death)	150

Tube*	Dilution of Ethylhydrocuprein in Broth	Strain			
		A	B	C	D
1	1 100,000	0	0	0	0
2	1 200,000	0	0	0	0
3	1 400,000	0	0	0	0
4	1 600,000	0	0	0	Growth
5	1 800,000	0	0	0	Growth
6	1 1,000,000	0	0	Growth	Growth
7	1 1,200,000	0	Growth	0	Growth
Control broth without ethyl hydrocuprein		Growth	Growth	Growth	Growth

* Tubes incubated forty eight hours at 37 5 C

The results given in Tables 1 and 2 show definitely that during the course of treatment in this case the pneumococci in the body become gradually resistant to the action of the ethylhydrocuprein The observations made in this case, together with the similar one made by us previously, not only demonstrate that this phenomenon of bacterial "fastness" may occur, but indicate that its occurrence is not infrequent

BACTERICIDAL ACTION OF PERICARDIAL FLUID

We have previously reported[1] that a pericardial exudate obtained post mortem from a patient who had received ethylhydrocuprein hydrochlorid by mouth for several days possessed bactericidal properties In the present series of cases the same phenomenon was demonstrated in pericardial fluids obtained post mortem from four other cases (Nos 2800, 2849, 2919 and 3031) In each case the pericardial fluid was allowed to clot and the supernatant fluid was then pipetted off and used for bactericidal tests Details of the tests of the pericardial fluid of two of these cases follow (Tables 3 and 4)

TABLE 3—Test of Bactericidal Powfr or Blood Serum and Pericardial Fluid from Hospital No 2800

Tube Number	Blood Serum Obtained*	Number of Colonics of Pneumococci per 0 5 C c When Plated†		
		Immediately	After 1½ Hours Incubation	After 19¼ Hours Incubation
1	Before ethylhydrocuprein	501	2,960	Confluent
2	12 hours after first dose	268	54	0
3	35 hours after first dose	421	121	0
4	Pericardial fluid obtained post mortem*	301	345	1

* The pericardial fluid contained many pneumococci and it and the serum were heated at 56 C for three fourths hour before testing to destroy the contained pneumococci
† Inoculation 0 001 c c of a four hour broth culture of Pneumococcus Type II

TABLE 4—Test of Bactericidal Power of Blood Serum and Pericardial Fluid from Hospital No 2919

Tube Number	Blood Serum Obtained	Number of Colonies of Pneumococci per 0 5 C c When Plated*		
		Immediately	After 1½ Hours Incubation	After 24 Hours Incubation
1	Before ethylhydrocuprein	1,200	2,400	Confluent
2	13 hours after first dose	1,200	Complete inhibition†	0
3	24 hours after first dose	800	Complete inhibition	84
4	69 hours after first dose	1,200	Complete inhibition	0
5	97 hours after first dose	1,000	Complete inhibition	0
6	Pericardial fluid obtained post mortem	2,000		26

* Inoculation 0 001 c c of a four hour broth culture of Pneumococcus Type I
† By complete inhibition of growth is meant no increase in the number of colonies

In Hosp No 2849 the pericardial fluid obtained post mortem showed pneumococcidal action, although the blood serum obtained during the ethylhydrocuprein treatment showed only temporary inhibition of growth

These observations show that when ethylhydrocuprein hydrochlorid is given by mouth according to the system of dosage used by us, it may pass into a serous sac (pericardial fluid) in amounts sufficient to exert a pneumococcidal action

TOXIC DISTURBANCES OF VISION

In one of the patients of our former series[1] the administration of ethylhydrocuprein hydrochlorid led to the production of alarming and severe retinitis, from which, however, the patient recovered In the present series eight patients complained of amblyopia, mild in three cases, more severe in five On discontinuing the ethylhydrocuprein, vision was restored in all those who survived the pneumonia, and in the two who died the vision was improved after the discontinuance of the drug Some details of these eight cases follow

Hosp No 2940—Housewife, aged 31, weight 74 2 kg

Past History—Unimportant

Present Illness—Chill, fever and pain in chest six days before admission

Status on Admission—Temperature 104 2 F, pulse 136, respirations 44 Consolidation of left upper lobe, leukocyte count 41,400 Sputum tenacious, gray and contained Pneumococcus Type IV Patient quite ill Blood culture positive (four colonies per cubic centimeter)

Course and Treatment—Ethylhydrocuprein hydrochlorid was started by mouth on the day of admission (seventh day of the disease) on a basis of 0 0269 gm per kilogram of body weight for the first twenty-four hours (1 × 0 5 gm + 10 × 0 15 gm) During the second twenty-four hours 0 15 gm was given every two hours One hour after the second of these latter doses the patient complained of slight blurring of vision, later the vision seemed normal and the hearing became slightly impaired, about the time of the seventh dose (second twenty-four hours) the patient complained of "waves" before her eyes and continuous ringing in the ears and one and one half hours after this dose she complaind that everything was "blurred and indistinct" The ethylhydrocuprein was therefore discontinued and after about eight hours the patient was seen by Dr W W Weeks His report on her visual condition stated that both disks were pale, that there were numerous small areas of edema scattered throughout the fundi, and that the patient could at this time count fingers at a distance of 6 feet The patient died two days after the ethylhydrocuprein was stopped The total amount of ethylhydrocuprein given was 3 05 gm

The bactericidal test of the serum of this case showed that pneumococcidal action for a stock strain of Pneumococcus Type II was present in the serum ten hours after the administration of the first dose of ethylhydrocuprein (plate poured immediately after inoculation showed 800 colonies, plate poured after one and one-half hours incubation, 400, and plate poured after twenty-four hours incubation was sterile) Pneumococcidal action was also present in serum obtained twenty-three hours after the initial dose The pneumococcidal action was no longer present in serum obtained shortly before death (ethylhydrocuprein having been discontinued for two days)

Hosp No 2885—Woman, cook, aged 42, weight 49 kg

Past History—Unimportant

Present Illness—Headache, pain in chest and vomiting two days before admission, followed next day by chill, little cough or expectoration

Status on Admission—Temperature 102 8 C, pulse 96, respirations 32 Involvement of right upper lobe posteriorly, leukocyte count 28,000, sputum slightly tenacious, not hemorrhagic, contained Pneumococcus Type II

Course and Treatment—Ethylhydrocuprein hydrochlorid was started by mouth on the day following admission, on a basis of 0 03 gm per kilogram of body weight for the first twenty-four hours ($1 \times 0\,45$ gm $+ 7 \times 0\,15$ gm), thereafter 0 15 gm every three hours After a total amount of 1 95 gm had been given, the patient complained that she could not see, the administration of ethylhydrocuprein was thereupon discontinued The pupils at this time were not dilated About one hour later the patient could distinguish the outline of persons Examination of the eyegrounds revealed no marked abnormalities On the following day the vision was much improved and the eyes were examined by Dr W W Weeks, who reported that there was indistinctness of both disk margins, the fundi were pale, the veins were somewhat dilated and tortuous, the arteries were of normal size, the vision was 20/20 in both eyes, and the fields were normal About this time the patient could distinguish colors and said she could see quite well This patient received, in addition to the ethylhydrocuprein, 770 c c of antipneumococcus serum, Type II, intravenously, in divided doses The temperature reached normal on the eighth day of the disease Pneumococcidal power for a stock strain of Pneumococcus Type I was present in the serum of this case within twelve hours after the initial dose of ethylhydrocuprein

Hosp No 2870—Housewife, aged 46, weight 56 9 kg

Past History—Two previous attacks of pneumonia

Present Illness—Three days before admission, chill, nausea, pain in chest, cough, blood-tinged sputum

Status on Admission—Consolidation of left lower lobe, well marked friction rub over entire precordial region, area of cardiac dulness not enlarged Temperature 105 1, pulse 112, respirations 34 Sputum bright, rusty-red, mucopurulent and contained Pneumococcus Type II

Course and Treatment—Ethylhydrocuprein hydrochlorid was started by mouth the day after admission (fourth day of disease) on a basis of 0 0263 gm per kilogram of body weight per twenty-four hours ($1 \times 0\,45$ gm $+ 7 \times 0\,15$ gm, thereafter 0 15 gm every two and a half hours) On the second day of treatment with ethylhydrocuprein the patient seemed slightly deaf and after 2 7 gm of ethylhydrocuprein had been given, on being questioned, the patient said that she could not see The pupils were widely dilated The ethylhydrocuprein was thereupon discontinued Three and a half hours later she said her sight was better, and in six hours after the last dose of ethylhydrocuprein she could distinguish objects The next day her sight was considerably better and the pupils less dilated The patient was seen by Dr W W Weeks a few hours after the ethylhydrocuprein treatment had been discontinued Dr Weeks reported as follows "Fingers can be seen 1 foot distant, visual fields moderately contracted, color not recognized, media clear, disks and fundi pale, veins engorged, arteries somewhat narrow" Dr Weeks' report two days later was as follows "vision 20/40+ with both eyes, visual fields contracted, especially on nasal side, red or green cannot be distinguished, disks pale, especially on temporal side, fundi not pale, condition of vessels same as on previous examination" Her vision gradually improved and was normal when she left the hospital Pneumococcidal power for a stock strain of Pneumococcus Type I appeared in the blood serum of this patient within twenty-four hours of the administration of the first dose of ethylhydrocuprein

Hosp No 2812—Woman, aged 74, weight 58 5 kg

Past History—Unimportant

Present Illness—The patient said that she had not felt well for several days before admission On the morning of the day before admission she felt very ill and had a temperature of 105 C, cough, blood-tinged sputum and pain in chest

Status on Admission—Temperature 104 1 F, pulse 94, respirations 40 Involvement of the left lower lobe, emphysema present, sputum tenacious, rusty and yielded on passage through a mouse, *Pneumococcus mucosus* (Type III)

Course and Treatment—Ethylhydrocuprein hydrochlorid was started by mouth on the day of admission, on a basis of 0 03 gm per kilogram of body weight per twenty-four hours (1 × 0 6 gm + 8 × 0 15 gm, thereafter 0 15 gm every two hours) After 0 9 gm of the ethylhydrocuprein had been given the patient complained of hearing roaring noises, and after 3 gm of ethylhydrocuprein she complained that she could not see The ethylhydrocuprein was then discontinued In six hours, however, she was able to count fingers and the next day her eyesight was much improved Eight hours after the patient complained of loss of vision she was seen by Dr W W Weeks, who reported that there was little change in the eyegrounds The patient died on the fifth day after admission to the hospital

Pneumococcidal action for a stock strain of Pneumococcus Type II appeared in this patient's serum six hours after the initial dose of ethylhydrocuprein

Hosp No 3015—Engineer, aged 47, weight 75 8 kg

Past History—Unimportant

Present Illness—Chill, vomiting, headache, and pain in chest thirty-six hours before admission

Status on Admission—Temperature 104 6 F, pulse 128, respirations 34 Consolidation of left lower lobe Sputum obtained on admission was tenacious, frothy, rusty and contained *Pneumococcus mucosus* (Type III) Urine gave a definite precipitin reaction with antipneumococcus serum Type III

Course and Treatment—Ethylhydrocuprein hydrochlorid was started by mouth eleven and one-third hours after admission to the hospital on a basis of 0 034 gm per kilogram of body weight per twenty-four hours (1 × 0 6 gm + 10 × 0 2 gm) After 2 4 gm had been given the patient complained that he could not see distinctly and the ethylhydrocuprein was discontinued At that time he could not see objects 1½ feet from his eyes, but could distinguish direct light from darkness, the pupils were somewhat dilated and did not react to light, the veins were engorged and the eyegrounds somewhat pale He had been questioned two and three-quarters hours previously as to whether he could see well, and replied that his vision was as good as normal, at that time he was partially deaf Twelve hours after the complaint that vision was impaired, the patient could read a watch at 2 feet and a ward clock at about 20 feet, and said he could see well, but that objects were a little blurred Later that day he was examined by Dr W W Weeks, whose report is abstracted as follows "Vision 20/40 + in both eyes, arteries injected, veins tortuous and engorged, left disk distinctly pale, especially the temporal half, visual fields restricted in both eyes, 10 degrees in right and 20 degrees in left, color is recognized by left eye but not by right" Three days later Dr Weeks reported as follows "Pupils equal, contracted, reacted readily to light during accommodation and on convergence, vision without correction O D 20/40 +, O S 20/210 with + 1 25 O D 20/20, with + 1 50 O S 20/20, concentric contraction for form, more in left eye, media clear, retina somewhat hazy near disks, so as to make disk margin a little indistinct, vessels normal except arteries of left eye which were somewhat smaller and more tortuous than those of right"

The temperature reached normal on the night of the day following admission to the hospital, but rose again thirty-six hours afterward and remained elevated for four days, although the pulse and respiration rates did not increase and the patient felt quite comfortable The patient recovered

The test of blood serum in this case showed pneumococcidal action for a stock strain of Pneumococcus Type II

Hosp No 2972—Man, complained of slight transient blurring of vision at times after the temperature had become normal, ethylhydrocuprein was discontinued (see Table 8 for details of the case)

Hosp No 2837—Man, complained of transient deafness, transient dimness of vision occurred after the temperature had become normal, ethylhydrocuprein was discontinued (see details of case in Table 8), the patient had an abrasion of the cornea and there was some inflammation of the right cornea on the morning that he complained of dimness of vision

Hosp No 2911—Woman, complained of dimness of vision and slight partial deafness after she had received 2 95 gm of ethylhydrocuprein hydrochlorid by mouth, both passed off after ethylhydrocuprein had been discontinued (for details of the case see Table 8)

In our entire series of seventy-five cases, nine, or 12 per cent of the patients, showed some degree of amblyopia Of all the patients treated with ethylhydrocuprein which are recorded in the literature, between 4 and 5 per cent suffered from amblyopia, and in two of these the impairment of vision was more or less permanent (Oliver[2] and Lorant[3]) In these latter cases, however, the dosage of the drug seems to have been excessive

RELATION OF NUMBER OF PNEUMOCOCCI TO CONCENTRATION OF ETHYLHYDROCUPREIN IN BACTERICIDAL TESTS

In the technic employed in the bactericidal tests we have used a fairly constant and rather small number of pneumococci per cubic centimeter It seemed advisable to determine whether or not the degree of bactericidal action would be the same when a larger number of pneumococci are employed Specimens of broth containing a small amount of ethylhydrocuprein in solution were therefore inoculated separately with two different amounts of the same culture and incubated at 37 5 C At frequent intervals plates were prepared and counts were made of the colonies which developed after incubation

Experiment 1—Fifty c c of bouillon containing ethylhydrocuprein hydrochlorid 1 to 1,000,000 were inoculated with 0 01 c c of a twenty-four hour culture of Pneumococcus Type II and a like amount of the same bouillon with 1 c c of the same culture Similarly, two flasks containing 50 c c of broth each but without ethylhydrocuprein were inoculated with 0 01 c c and 1 c c of the culture, respectively, as controls All four cultures were incubated at 37 5 C and bacterial counts were made at frequent intervals by making suitable dilutions and pouring plates with 20 c c dextrose agar The results of the experiment are given in Table 5

2 Oliver, G H Brit Med Jour, 1916, **1**, 580
3 Lorant, L Deutsch med Wchnschr, 1916, **42**, 1355

TABLE 5—Number of Pneumococci in Relation to Action of Ethylhydrocuprein Hydrochlorid

Incubation		Broth without Ethylhydrocuprein Inoculation 0 01 C c		Broth with Ethyl hydrocuprein 1 1,000,000 Inoculation 0 01 C c		Broth without Ethylhydrocuprein Inoculation 1 0 C c		Broth with Ethylhydrocuprein 1 1,000,000 Inoculation 1 0 C c	
Hours	Minutes	No of Viable Pneumococci per 0 5 C c	Log	No of Viable Pneumococci per 0 5 C c	Log	No of Viable Pneumococci per 0 5 C c	Log	No of Viable Pneumococci per 0 5 C c	Log
0	0	28,000	4 447	19,050	4 379	2,455,000	6 390	2,450,000	6 389
2	0	19,300	4 285	11,450	4 05	2,870,000	6 457	1,685,000	6 226
4	0	9,750	3 989	475	2 676	7,050,000	6 848	1,005,000	6 002
5	30	11,450	4 058	37	1 568	22,500,000	7 352	625,000	5 795
7	0	11,850	4 073	3	0 047	26,500,000	7 423	370,000	5 568
9	0	34,500	4 537	0	0	49,500,000	7 694	210,000	5 322
11	35	625,000	5 795	0	0	67,500,000	7 829	100,000	5 000
25		49,500,000	7 694	0	0	55,500,000	7 744	240,000	5 380
48						51,000,000	7 707	45,000,000	7 653

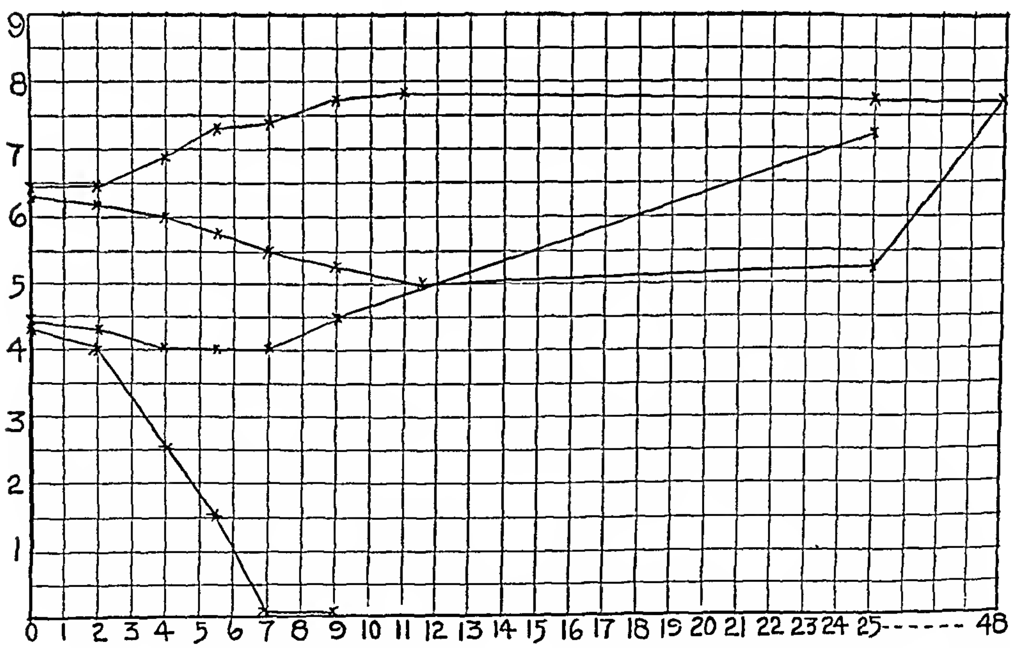

Diagram illustrating Experiment 1 Time in hours as abscissae at bottom, and at left logarithms of numbers of viable pneumococci per 0 5 c c as ordinates A, Broth without ethylhydrocuprein Inoculation 0 01 c c B, Broth with ethylhydrocuprein (1 1,000,000) Inoculation 0 01 c c C, Broth without ethylhydrocuprein Inoculation 1 c c D, Broth with ethylhydrocuprein 1 1,000,000 Inoculation 1 c c

This experiment shows that while 19,050 pneumococci were all killed in nine hours in broth containing ethylhydrocuprein 1 to 1,000,000, 2,450,000 pneumococci were reduced to 100,000 in eleven hours and thirty-five minutes, but the surviving pneumococci were able to grow and in forty-eight hours multiplied approximately to the same extent (45,000,000) as in the control broth culture The logarithms of the bacterial count are shown in Table 5 The results of Experiment 1 are shown graphically by plotting curves (Fig 1), employing the time in hours as abscissa and the logarithms of the numbers of viable pneumococci per 0 5 c c of culture as ordinates

PENETRATION OF ETHYLHYDROCUPREIN INTO FIBRINOUS EXUDATES

In the course of our clinical and experimental observations on ethylhydrocuprein, we have received the impression that the drug does not readily penetrate the alveolar exudate The concentration of ethylhydrocuprein in the blood of patients receiving the drug, according to the dosage most commonly used by us, is about 1 in 500,000, as judged by the pneumococcidal action of the serum in the test tube If ethylhydrocuprein in this concentration were to thoroughly penetrate the alveolar exudate, it should destroy the pneumococci present therein, and one might therefore anticipate a shortening of the duration of the disease Since the duration of the disease is not shortened the following experiment was devised to study the power of ethylhydrocuprein to penetrate a fibrinous clot

Experiment 2—Fifty c c of normal rabbit blood were drawn into 1 c c of sterile 20 per cent sodium citrate solution ($2Na_3C_6H_5O_7 H_2O$) and centrifugalized The supernatant plasma was drawn off and inoculated with a stock strain of Pneumococcus Type II (0 0001 c c of an eighteen-hour culture to 1 c c plasma) and 1 1 c c of sterile 9 5 per cent calcium chlorid solution was then added and thoroughly mixed The mixture was transferred to sterile cotton-plugged glass tubes 0 9 cm in diameter, 2 c c being placed in each tube A firm clot formed at the bottom of each tube in about one to one and a half hours at room temperature To one of the tubes 1 6 c c of 0 85 per cent saline solution was then added, covering the clot, and, in a similar manner, to each of the remaining tubes there was added 1 6 c c of saline solution containing a given concentration of ethylhydrocuprein hydrochlorid The tubes were kept at room temperature for one-half hour, then incubated for twenty hours at 37 5 C, and examined The number of organisms used for the incubation had been so chosen that the control tube which contained no ethylhydrocuprein showed small discrete colonies uniformly "peppering" the clot In the tubes containing the more concentrated ethylhydrocuprein solutions no growth occurred in the upper portions of the clot This was interpreted as due to the effect of the ethylhydrocuprein penetrating the clot in effective concentration to the depth of the zone of inhibition The depth of the zone of inhibition bore a definite relationship to the concentration of the ethylhydrocuprein in the supernatant fluid The zones of inhibition in the various tubes were measured and the results are shown in Table 6

TABLE 6—INHIBITION BY ETHYLHYDROCUPREIN OF GROWTH OF PNEUMOCOCCI IN FIBRINOUS CLOTS

Dilution of Ethylhydrocuprein	Depth in Mm of Zones of Inhibition of Growth	Dilution of Ethylhydrocuprein	Depth in Mm of Zones of Inhibition of Growth
1 100	10	1 10,000	5 5
1 500	9 5	1 50,000	3 5
1 1,000	9 0	1 100,000	2 5
1 5,000	6 0	1 200,000	1 75
1 10,000	5 5	1 300,000	1 25
1 50,000	3 5	1 400,000	1 0
1 100,000	2 5	1 500,000	0 0
1 500,000	0 0	1 600,000	0 0
1 1,000,000	0 0		
Control with saline	0 0	Control with saline	0 0

These experiments demonstrate that optochin, in the concentrations attainable with any degree of safety in the blood plasma of patients (about 1 in 500,000), possesses little power to penetrate a fibrinous clot It is, therefore, possible that pneumococci in the interior of a pneumonic exudate may escape the action of ethylhydrocuprein, even though the drug be present in the blood stream in considerable concentration

CLINICAL OBSERVATIONS

In discussing the effect of ethylhydrocuprein on the clinical course of the disease, the patients treated during the two years will be considered as one series As previously, they will be analyzed from the standpoint of (*a*) the duration of the disease, (*b*) the occurrence of "spread" of involvement of lobes hitherto unaffected, (*c*) the effect of treatment on pneumococcemia and (*d*) mortality with reference to the immunologic classification of the infecting strain of pneumococcus

(*a*) *Effect on Duration of Disease*—Using the occurrence of a rectal temperature below 100 F as a criterion for the termination of the acute attack, an arbitrary but serviceable standard, the average duration of the disease in all the recovered patients was eight days No marked shortening, therefore, of the course of the disease can be said to have occurred in our series

(*b*) *Occurrence of "Spread" of Pulmonary Lesion*—Of the 75 cases, 20, or 26 6 per cent, showed a "spread" during treatment In 14 of these 20 cases the serum of the patient possessed bactericidal power at the time the spread took place, this may be taken as presump-

tive evidence that the drug, although circulating in the blood in amounts sufficient to destroy pneumococci, does not pass into the alveolar spaces or exudate in amounts sufficient to destroy the bacteria there or inhibit their growth to any marked extent

(*c*) *Pneumococcemia*—In 23, or 30 6 per cent of the 75 cases, viable pneumococci were present in the circulating blood at some time during the course of the disease In many instances there were only a few pneumococci present, whereas in others there was a comparatively heavy blood infection In 19 of the 23 cases the blood culture was positive before ethylhydrocuprein treatment was begun, in 4 of these the blood culture became negative during treatment with ethylhydrocuprein alone, 9 of the cases showed a progressively increasing number of micro-organisms while under treatment, and the remaining 6 died without subsequent blood cultures having been made When in addition to ethylhydrocuprein immune serum was used in treatment, the number of pneumococci in the circulating blood was always reduced after the first administration of serum, but in one instance the number of micro-organisms later increased even though the patient received both ethylhydrocuprein and serum In 4 instances the blood culture was negative at the time the ethylhydrocuprein treatment was instituted, but became positive later From these results it may be stated that no marked beneficial effect of ethylhydrocuprein treatment was observed on the pneumococcemia of lobar pneumonia

(*d*) *Mortality*—Of the 75 patients treated, 28 died—a mortality rate of 37 3 per cent Some of the patients were inadequately treated, judging from the production of pneumococcidal power in the serum Moreover, in several cases treatment was instituted less than twenty-four hours before death and at a time when the patients were critically ill, the duration of administration of the drug in these cases was, therefore, too short to be of any value, considering the time required for its absorption and action If all the patients who are known to have been inadequately treated, regardless of whether they died or recovered, be excluded, and also those cases in which treatment was instituted within twenty-four hours of death, or in which crisis occurred before the serum acquired bactericidal power, there would remain 51 cases, of whom 16 patients died — a mortality of 31 3 per cent Of the 24 cases excluded from consideration 12 patients died and 12 recovered The mortality rate in the 51 adequately treated patients, 31 3 per cent, does not show any considerable therapeutic effect from the use of the drug

It should be stated that the series probably represents a group of very severe cases, for it is composed for the most part of cases due to infection with pneumococci of Types II and III, which we know are

the types responsible for the highest mortality rates When the expected mortality in each of these groups (untreated) is compared with that actually encountered in the patients treated with ethylhydrocuprein, we find some reduction of mortality rate in the cases infected with pneumococci belonging to Group III, and no reduction in the cases due to pneumococci of Groups II and IV This will be seen from a study of Table 7, in which the cases are arranged according to the type of infecting pneumococcus and in which the mortality obtained in the various groups in our series is contrasted with that obtained in a large series of patients not treated specifically and observed in different clinics[1] One is forced to conclude from these figures that treatment with ethylhydrocuprein hydrochlorid failed to cause any reduction in the general mortality rate

TABLE 7—Mortality Among Patients Treated with Ethylhydrocuprein Hydrochlorid Compared with That of Patients Not Specially Treated

Pneumococcus Type	Number of Patients Treated with Ethylhydrocuprein	Recovered	Died	Mortality Rate Per cent	Average Mortality Rate in Patients Not Specifically Treated
II	27	19	8	29 6	28
III	17	10	7	41 1	56
IV	6	5	1	16 6	16
Unclassified	1	1	0	0	
	51	35	16	31 3	About 26

Of the 75 patients treated with ethylhydrocuprein, 14 in which the disease was caused by pneumococci belonging to Group II were treated, in addition, with the type homologous antipneumococcus serum This agent was used in the form of the whole serum intravenously or the concentrated "extract"[4] of the serum subcutaneously and intravenously Of these 14 patients 10 recovered and 4 died, giving a mortality rate of 28 5 per cent, so that no reduction in the mortality rate was observed in cases of lobar pneumonia due to Pneumococcus Type II as a result of treatment with ethylhydrocuprein and antipneumococcus serum The number of patients treated with serum and ethylhydrocuprein is too small, however, to permit of final conclusions on this point

DISCUSSION

The experimental studies which we have here discussed and those previously reported show that ethylhydrocuprein hydrochlorid fulfills at least some of the requirements of a chemotherapeutic agent in lobar pneumonia Even in high dilutions it kills the pneumococcus in

4 Chickering, H T Jour Exper Med, 1915, 22, 248

the presence of body fluids. It is capable of being absorbed from the gastro-intestinal tract, and when injected into the muscles (Case 2947, Table 8) may pass into the blood stream. Moreover, when a sufficient amount is administered by mouth, represented by 0.024 to 0.028 gm. per kilogram of body weight per twenty-four hours, the blood serum becomes pneumococcidal in vitro, and furthermore, when such a condition obtains in the blood, the pericardial fluid also becomes pneumococcidal. The amount of the drug which it is necessary to administer in order to achieve this result, however, cannot always be given with safety to the patient, for in one instance in our series of cases total blindness lasting six days resulted, and in eight other instances there occurred visual symptoms of sufficient gravity to make the discontinuance of the drug necessary. A study of Table 8 would seem to suggest that where there is a comparatively heavy septicemia (for example, 100 colonies per 1 c.c. or over) a dosage of ethylhydrocuprein represented by 0.026 gm. per kilogram of body weight per twenty-four hours may be insufficient to produce pneumococcidal actions in the blood serum. It is possible that in such instances the drug may be fixed by the circulating pneumococci (Case Nos. 2845 and 2892). In only one case (No. 2822) which received 0.026 gm. of the hydrochlorid of the drug, or over, per kilogram of body weight per twenty-four hours in suitably divided doses did pneumococcidal action fail to appear in the serum.

When the cases in our series are analyzed from the standpoint of the effect of the drug on the duration of the disease, on the occurrence of "spread" of the lesion to previously uninvolved lobes of the lung, on the pneumococcemia and on the mortality rate, the results do not afford much support for the routine use of this drug in the treatment of acute lobar pneumonia.

It seems to us that the main reason why ethylhydrocuprein has not produced more striking results in the treatment of lobar pneumonia is because the toxicity of the drug is such as to keep the limits of dosage below the limits of effectiveness. If larger doses could be safely employed, it would be possible greatly to increase the amount of ethylhydrocuprein circulating in the blood. This would in turn undoubtedly increase the rate and degree of the resulting pneumococcidal action in the blood and might conceivably lead to a greater penetration of the drug into the consolidated portions of the lung. Our tests show that ethylhydrocuprein may be administered to patients in amounts sufficient to cause the serum to acquire pneumococcidal power. With the dosage that may be safely employed, however, the serum exhibits its bactericidal activity only at a slow rate, considerable time being required. Because of this fact the pneumococci in the body may be exposed for considerable time to concentrations of the drug insufficient to cause their destruction, particularly when they are protected by the

TABLE 8—S[illegible]

Hospital Case Number	Age	Weight, Kg	Type of Infecting Pneumococcus	Day of Disease When Ethylhydrocuprein Treatment Was Begun	Lung Involvement on Admission	Blood Culture Before Treatment	Method of Dosage of Ethylhydrocuprein in Periods of 24 Hrs * Gm	Amount of Ethylhydrocuprein per Kilogram of Body Weight per 24 Hrs Gm	Total Amount of Ethylhydrocuprein in Gram[s]
2753	27	55 8	II	3	L L	Sterile	0 45+7×0 15, 10×0 15	0 0269	5 7
2754	13	39 6	II	8	L U L L		0 3+7×0 1, 10×0 1	0 0252	2 3
2783	48	63 3	III	7	R U R L	Positive, 325 col per 1 0 c c	0 45+0 25+0 3, 2×0 15, base		1 3
2786	34	42 7	II	8	R U	Sterile	0 3+0 2+7× 0 10, 10×0 1, base	0 028	2 2
2797	67	78 2	III	2	R U	Sterile	0 6+2×0 25+6 ×0 15, 11×0 2	0 023	10 8
2800	42	78 9	III	4	L L	Sterile	0 6+0 3+8× 0 2, 1 65 in 2nd 24 hrs	0 03	4 1[illegible]
2812	74	58 5	III	2	L L	Sterile	0 6+8×0 15, 12×0 15	0 03	3 0
2822	13	37 2	II	6	L L	Sterile	0 2+7×0 1, 9× 0 1, 10×0 1	0 0241	3 6
2762	23	70 0	III	3	R L	Sterile	0 45+8×0 15, 3×0 5 per rectum	0 0235	3 1[illegible]
2825	50	69 0	II	2	L L	Positive, 3 col per 1 c c	0 6+8×0 15, 12×0 15	0 026	6 5
2827	29	52 6	II	3	L L L U	Positive, 2,000 cols per 1 c c	0 45+2×0 15	0 0285	0 75
2831	35	57 0	II	5	L L	Sterile	0 45+7×0 15, 10×0 15	0 0263	1 65
2834	28	58 4	II	5	L L	Sterile, 16 hrs after ethylhydrocuprein positive—12 col per 1 c c	0 5+0 2+6× 0 15, 9×0 15, 10×0 15	0 0274	9 05
2837	48	46 0	III	2	R L	Sterile	0 45+7×0 15, 7×0 2	0 0326	2 9

* Given by mouth unless otherwise stated, hydrochlorid used unless otherwise stated

OF CASES

Time of Appearance of Bactericidal Action in Serum after Initial Dose of Ethylhydrocuprein	Duration of Disease in Days	Toxic Symptoms Referable to Ethylhydrocuprein	Complications	Occurrence of "Spread" During Treatment	Result	Remarks
Not studied	7	None	None	None	Recovered	
Not studied	10	None	Pericarditis	None	Death	
No B A	7	None	Pericarditis	None	Death	Blood culture 8 hours after treatment showed innumerable colonies per 0 5 c c blood
No B A	9	None	None	None	Recovered	
20 Hrs	7	None	None	Spread to right lower	Death	
11 Hrs	6	None	None	None	Death	Blood culture 24 hours after treatment was begun showed 23 colonies per 1 0 c c blood, pericardial fluid showed bactericidal action
6 Hrs	6	Temporary blindness, deafness and tinnitus	None	None	Death	Ethylhydrocuprein discontinued on account of eye symptoms
No B A, slight temporary inhibition	10	None	None	None	Recovered	
5 Hrs	5	Persistent vomiting, partial deafness	None	None	Recovered	
5 5 Hrs	5	None	None	None	Death	Progressive increase in septicemia during treatment "Fast" strains recovered from blood, antipneumococcus serum 85 c c intravenously on last day
Not studied	4	None	None	None	Death	
11 Hrs	6	None	None	None	Recovery	75 c c antipneumococcus serum intravenously
11 Hrs	11	None	None	Spread to right lower	Death	Active maniacal delirium Blood culture positive 16 hours after ethylhydrocuprein was started, 1,015 c c antipneumococcus serum intravenously
Within 24 Hrs	4	Transient deafness, slight dimness of vision after Temp had become normal	None	None	Recovery	Ethylhydrocuprein discontinued after temp became normal on account of eye symptoms Eye grounds apparently normal on ophthalmoscopic examination at time patient complained of dimness of vision

TABLE 8—SUMMARY

Hospital Case Number	Age	Weight, Kg	Type of Infecting Pneumococcus	Day of Disease When Ethylhydrocuprein Treatment Was Begun	Lung Involvement on Admission	Blood Culture Before Treatment	Method of Dosage of Ethylhydrocuprein in Periods of 24 Hrs * Gm	Amount of Ethylhydrocuprein per Kilogram of Body Weight per 24 Hrs Gm	Total Amount of Ethylhydrocuprein in Grams	Duration of Treatment in Days
2838	45	48 8	III	4	R L	Sterile	0 5+5×0 2, 8×0 2, 6×0 25	0 0307	7 6	5
2845	46	40 4	II	5	R U	Positive, 1,000 col per 1 c c	0 5+4×0 25, 6×0 25	0 0371	2 0	1⅓
2849	42	94 4	III	4	R U	Positive, 1 col in 3 c c	0 5+4×0 25, 6×0 25	0 0158	2 0	1⅓
2865	23	60 4	II	4	L U	Sterile	0 45+7×0 15, 10×0 15	0 0248	5 25	4
2869	31	66 6	II	2	R L	Positive, 400 col per 1 c c	0 45+7×0 15, 10×0 15	0 0225	5 8	4
2870	46	56 8	II	4	L L	Sterile	0 45+7×0 15, 8×0 15	0 0263	2 7	2
2879	26	79 0	II	3	L L	Positive	0 5+9×0 15, 10×0 15	0 0234	3 45	2
2885	42	49 0	II	3	R U	Sterile	0 45+7×0 15	0 0300	1 95	1½
2886	21	59 8	II	4	L U	Sterile	0 45+7×0 15, 11×0 15	0 0250	5 25	4
2892	41	59 0	II	5	R U	Positive, 100 col per 1 c c	0 45+7×0 15, 10×0 15	0 0254	2 25	1½
2890	28	35 5	II	4	R L	Positive, 3 col per 1 c c	0 45+8×0 15, 10×0 15	0 0464	5 4	4
2897	34	59 0	II	4	L U	Sterile	0 45+7×0 15, 10×0 15	0 0254	6 0	4
2898	32	53 2	III	5	L L	Positive, 120 col per 1 c c	0 45+7×0 15, 10×0 15	0 0283	3 75	3
2911	50	74 2	III	3	R U	Sterile	0 45+7×0 15+1×0 1, at rate of 10×0 15 thereafter	0 021	2 95	2

* Given by mouth unless otherwise stated, hydrochlorid used unless otherwise stated

OF CASES

Time of Appearance of Bactericidal Action in Serum after Initial Dose of Ethyl hydrocuprein	Duration of Disease in Days	Toxic Symptoms Referable to Ethylhydrocuprein	Complications	Occurrence of "Spread" During Treatment	Result	Remarks
Within 24 Hrs	9	None	None	None	Recovery	
No B A, temporary inhibition only	7	None	None	None	Death	Pericardial fluid showed bactericidal action, 300 c c antipneumococcus serum intravenously
No B A	5	None	None	None	Death	Blood culture before death, 1,000 colonies per 1 0 c c blood
Within 24 Hrs	7	None	None	None	Recovery	
No B A	6	None	None	Spread to right upper	Death	Blood culture constantly positive, 10,000 colonies per 1 0 c c just before death, 580 c c antipneumococcus serum intravenously
Within 24 Hrs	9	Transient amblyopia and deafness	None	None	Recovery	Ethylhydrocuprein discontinued on onset of amblyopia
No B A, slight temporary inhibition	5	None	None	None	Recovery	Blood culture became negative during treatment, 440 c c antipneumococcus serum intravenously
Within 12 Hrs	8	Transient amaurosis and tinnitus	None	None	Recovery	Ethylhydrocuprein discontinued on account of eye symptoms, 770 c c antipneumococcus serum intravenoutly, delayed resolution
Within 12 Hrs	8	Slight deafness	None	None	Recovery	
No B A, slight temporary inhibition	7	None	None	Spread to right lower	Death	Blood culture before death, 600 colonies per 1 0 c c blood
Within 24 Hrs	8	None	Pneumococcal meningitis	Spread to left lower	Death	Blood culture 18 hours after ethylhydrocuprein was commenced showed 14 colonies per 1 c c, 1,300 c c serum intravenously, 80 c c serum intraspinously, 30 c c concentrated serum subcutaneously
Within 12 Hrs	8	None	None	None	Recovery	380 c c serum intravenously, 74 c c conc serum subcutaneously
Within 24 Hrs	8	None	None	Spread to right lower	Death	
Complete inhibition	8	Temporary blurring of vision and temporary partial deafness	None	None	Recovery	Ethylhydrocuprein discontinued on account of eye symptoms

TABLE 8—SUMMARY

Hospital Case Number	Age	Weight, Kg	Type of Infecting Pneumococcus	Day of Disease When Ethylhydrocuprein Treatment Was Begun	Lung Involvement on Admission	Blood Culture Before Treatment	Method of Dosage of Ethylhydrocuprein in Periods of 24 Hrs * Gm	Amount of Ethylhydrocuprein per Kilogram of Body Weight per 24 Hrs Gm	Total Amount of Ethylhydrocuprein in Grams	Duration of Treatment in Days
2919	35	49 8	III	4	L L	Sterile	0 45+7×0 15, 10×0 15	0 03	6 30	4
2922	30	58 0	II	4	L L	Sterile	0 45+7×0 15, 10×0 15	0 0258	11 1	8
2926	19	46 0	II	5	R U	Sterile	0 45+5×0 15, 7×0 15	0 026	3 0	2½
2927	22	56 4	III	3	R L	Sterile	0 45+7×0 15, 8×0 15	0 0265	4 95	4
2940	31	74 2	IV	7	L U	Positive, 4 col per 1 c c	0 5+10×0 15, 12×0 15	0 0269	3 05	2
2943	22	44 4	II	5	R L	Sterile	0 4+8×0 1, 12×0 1	0 027	4 9	4
2946	28	62 6	II	4	R U	Sterile	0 5+8×0 15, 12×0 15	0 0271	12 8	8
2947	51	70 4	III	6	R L	Positive	0 7 intramuscularly + single dose of 1 8 gm intramuscularly	0 0355	9 9	5
2973	40	50 2	III	3	R U	Sterile	0 45+7×0 15, 10×0 15	0 0375	3 15	3
2972	19	55 6	II	1	L L	Sterile	0 45+7×0 15, 10×0 15	0 0269	6 55	4½
2991	49	71 2	II	2	R L	Sterile	0 45+9×0 15, 6×0 3	0 025	14 4	8
3006	35	46 8	II	3	R L	Sterile	0 45+7×0 15, 10×0 15	0 032	7 8	5
3015	47	75 8	III	3	L L	Sterile	0 6+10×0 2	0 034	2 2	1
2868	20	57 0	II	5	R L	Sterile	0 45+7×0 15	0 0263	1 5	1
3031	38	57 0	II	3	L L	Positive, 80 col per 1 c c	0 45+8×0 15, 9×0 15, 10×0 15	0 028	6 3	5½

* Given by mouth unless otherwise stated, hydrochlorid used unless otherwise stated

of Cases

Time of Appearance of Bactericidal Action in Serum after Initial Dose of Ethylhydrocuprein	Duration of Disease in Days	Toxic Symptoms Referable to Ethylhydrocuprein	Complications	Occurrence of "Spread" During Treatment	Result	Remarks
Within 12 Hrs	9	None	None	Spread	Death	Pericardial fluid showed bactericidal action, blood culture sterile post mortem
12 Hrs	14	None	None	Spread to left upper	Recovery	197 c c conc serum subcutaneously
12 Hrs	8	Slight deafness	None	None	Recovery	
12 Hrs	6	Temporary deafness	None	Spread to left upper	Recovery	
10 Hrs	11	Dimness of vision and tinnitus	None		Death	Ethylhydrocuprein discontinued on account of eye symptoms, eye symptoms disappeared
10 Hrs	10	None	None	Spread to right upper	Recovery	
12 Hrs	12	None	None	Spread to right lower	Death	Blood culture shortly before death yielded innumerable colonies
6 5 Hrs	?	None	Empyema	Spread to left lower	Operation, death 60 days after admission	Blood culture became negative, intermission of 90⅝ hours in ethylhydrocuprein treatment after 2 5 gm had been given
Within 24 Hrs	6	Temporary deafness	None	None	Recovery	
Within 24 Hrs	6	Slight transient blurring of vision after temp had become normal	None	None	Recovery	
Not studied	9	Temporary deafness	Delayed resoluton	None	Recovery	
Within 12 Hrs	8	None	None	Spread to left lower	Death	
Within 12 Hrs	?	Temporary blindness	None	None	Recovery	Ethylhydrocuprein discontinued on account of visual symptoms
Not studied	12	None	None	None	Recovery	Ethylhydrocuprein discontinued because it was thought that patient had had crisis
Within 12 Hrs	8	None	None	None	Death	Strain obtained just after death was not "fast" to ethylhydrocuprein, pericardial fluid obtained post mortem showed pneumococcidal action for Type I pneumococcus

comparative impenetrability of a solid pneumonic exudate Under such circumstances, as we have shown, pneumococci may become resistant or "fast" to the action of the drug

As our experiments indicate, there seems to be some relationship between the number of pneumococci and the concentration of ethylhydrocuprein which is required to completely kill them Thus, in test tube experiments it has been shown that whereas a given amount of the drug in solution is sufficient to destroy a given number of pneumococci per unit volume, the same amount of drug is not able to destroy 100 times this number in the same volume Inasmuch as we cannot estimate in any human case the number of pneumococci which it is necessary to destroy, it is quite conceivable that much larger amounts of the drug than we have found it safe to administer may be necessary to produce the required concentration in the body fluids

Finally, it is probable that in the concentration which may safely be attained in the blood stream of the patient (about 1 in 500,000), the drug does not penetrate the alveolar exudate to any marked degree and therefore cannot kill the pneumococci there present

Our conception of the present status of ethylhydrocuprein therapy in lobar pneumonia is, then, that while much of the experimental evidence is favorable, the clinical results that have been obtained are scarcely sufficient to warrant the routine administration of a drug the use of which may result in damage to vision Probably the drug would be efficient if it could be given in larger amounts As a "lead" in chemotherapy the drug is of great value, synthetic study of the quinin alkaloids should be made for a compound possessing greater pneumococcidal power in the presence of body fluids, greater velocity of action on pneumococci and less toxicity Such a compound should, in addition, possess the power of rapid and easy penetration into the alveolar exudate With such a drug at our disposal we might expect in lobar pneumonia something approaching a *therapia sterilisans magna*

CONCLUSIONS

1 Ethylhydrocuprein (optochin) base is absorbed with difficulty into the blood stream from the gastro-intestinal tract, the hydrochlorid of the drug is readily absorbed

2 During treatment with ethylhydrocuprein pneumococci in the human body can gradually become "fast" or resistant to its action

3 The pericardial fluid obtained post mortem from patients treated with ethylhydrocuprein hydrochlorid showed pneumococcidal power

4 The serum of one patient who received a very large dose of ethylhydrocuprein hydrochlorid intramuscularly showed pneumococcidal power (Case 2947, Table 8)

5 Among seventy-five patients treated with ethylhydrocuprein there were nine who showed some degree of amblyopia (12 per cent), this was mild in three cases and more severe in six In all those who recovered from the pneumonia, the eye symptoms disappeared completely after the administration of the drug had been discontinued

6 The systematic use of ethylhydrocuprein (optochin) in the treatment of seventy-five cases of acute lobar pneumonia due to pneumococci did not lead to any noteworthy therapeutic benefit The failure of the ethylhydrocuprein treatment to influence favorably the course of the disease is probably due to the following

(*a*) It is impossible to administer a sufficient amount of the drug to produce an effective concentration in the blood stream without at the same time exposing the patient to the danger of toxic action

(*b*) The rate of the pneumococcidal action of ethylhydrocuprein is too slow in the concentrations which may be attained in the blood stream of the patient with any degree of safety, pneumococci, therefore, may gain access to the circulating blood at a greater rate than they are destroyed therein, even though the serum show pneumococcidal action

(*c*) In the concentrations which are safely attained in the body fluids the drug probably penetrates but poorly into the alveolar exudate

7 The routine use of ethylhydrocuprein in the treatment of acute lobar pneumonia cannot be recommended

CIRCULATORY REACTIONS TO EXERCISE DURING CONVALESCENCE FROM INFECTIOUS DISEASE*

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The return of patients to normal after pneumonia, typhoid and typhus fevers and the other infectious diseases is a phenomenon with which we all are familiar clinically, yet convalescence up to the present has not been investigated in any exact or quantitative way The length of time during which convalescent patients are confined to bed and the resumption of normal life are graduated very differently by different practitioners In view of this great variation in procedure any accurate or quantitative method by which we could observe the stage of a patient's convalescence would be very desirable

At present the need for such an accurate method of following a patient's convalescence is rendered acute by the military situation We have in training a great number of young men, many of whom are being attacked by infectious diseases In the treatment of these patients efficiency demands that their absence from military duties shall be sufficient for complete convalescence but shall not be prolonged unduly beyond the proper time If the proper time for convalescence is to be determined, as it is at present, solely by the opinion of the attending physician, it is highly probable that some soldiers will be returned to active service too soon and some too late In the former case we may do the patient serious injury, in the latter case we shall have wasted time, attention and hospital accommodation at a time when all of these are in great demand With these considerations in mind we have conducted a series of experiments on patients recovering from acute infections

We have confined our attention to the circulatory system because of the following considerations Once the original infection has been overcome, the recovery of the patient means really the recovery of the patient's ability to do muscular work, and the recovery of the patient's ability to do muscular work is essentially a circulatory rather than a muscular phenomenon The ordinary person in health overtaxes his circulation long before he exhausts his skeletal musculature The convalescent from infectious disease is limited in his exercise not by what his muscles can do but what his heart can do This is obvious when we consider that the serious pathologic effects of overexertion, both in health and in disease, are not muscular but circulatory We cannot

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* From the cardiographic laboratory of the Mount Sinai Hospital

easily overwork a skeletal muscle, because it has a very efficient safety device—refusal to respond We can overwork the circulatory system, because refusal to respond adequately on its part does not result in immediate cessation of work Therefore, it seemed logical to determine the circulatory reactions following muscular work at different periods during convalescence to see if we could discover any change in these reactions which might afford a criterion of the return to normal of the circulation

The patients whose recovery we have followed have all been men between the ages of 21 and 45 years There are ten cases in our series seven pneumonias, one pleurisy, one typhoid fever, one typhus fever

Our procedure has been as follows The pulse rate was taken several times until it reached a constant figure The systolic blood pressure was read by auscultation (using a mercury sphygmomanometer) until it reached its normal level Then the patient performed a definite amount of work The pulse rate was counted for 15 seconds immediately after the work and, at the end of 110 seconds, it was counted again for 20 seconds From these two figures the rates immediately after exercise and at the end of 120 seconds were calculated The systolic blood pressure was taken by the method described by Barringer[1] and also, in some cases, by the method of Cotton, Rapport and Lewis [2] Our exercises have consisted in sitting up in bed and in flexing and swinging dumb-bells of various weights We have calculated the work done in foot-pounds The calculation of work done is fairly accurate and the error is constant for the same patient, so that slight inaccuracies will not vitiate our conclusions

The method of Barringer[1] consists in taking the systolic pressure before exercise and then taking three readings after exercise—the first between 25 and 30 seconds, the second between 55 and 60 seconds, the third between 85 and 90 seconds—the endeavor being to make the readings as close to 30, 60 and 90 seconds as possible The method described by Cotton, Rapport and Lewis[2] consists in taking the first reading as soon after exercise as possible and in taking numerous readings thereafter at very short intervals These readings, when plotted, give us a curve which shows the variations in the systolic pressure after exercise For reasons which we give later we have used Barringer's method in the majority of our experiments Our technic has been standardized during the past four months by testing the circulatory reactions of a number of normal persons and of many patients suffering from cardiac insufficiency

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1 Barringer, T B, Jr Studies of the Heart's Functional Capacity, The Archives Int Med, 1917, **20**, 829

2 Cotton, T F, Rapport, D L, and Lewis, T After Effects of Exercise on Pulse Rate and Systolic Blood Pressure in Cases of "Irritable Heart," Heart, 1917, **6**, 269

Barringer believes that a "delayed rise" ("delayed summit," Cotton, Rapport and Lewis) indicates the overtaxing of the cardiac reserve power A reading at sixty seconds after exercise which is 4 mm or more higher than the reading at thirty seconds has been taken as indicative of a delayed summit We have generally been able to produce a delayed summit much more pronounced than this minimum

The following typical normal series of tests will illustrate the method of testing and recording The subject was a normal man, 26 years old, weighing 160 pounds

His systolic blood pressure at rest was		130
He swung two 10-pound dumb-bells 10 times (Calculated work = 2,400 foot-pounds)		
His systolic pressure after work was—	at 30 seconds	150
	at 60 seconds	140
	at 90 seconds	130
In 5 minutes his systolic pressure at rest was constant at		120
He swung two 10-pound dumb-bells 25 times (Calculated work = 6,000 foot-pounds)		
His systolic pressure after work was—	at 30 seconds	152
	at 60 seconds	152
	at 90 seconds	144
In 5 minutes his systolic pressure at rest was constant at		125
He swung two 10-pound dumb-bells 30 times (Calculated work = 7,200 foot-pounds)		
His systolic pressure after work was—	at 30 seconds	150
	at 60 seconds	164 (delayed summit)
	at 90 seconds	156

In tabulated form the record reads as follows

130		120		125	
2 × 10 S 10	(2,400)	2 × 10 S 25	(6,000)	2 × 10 S 30	(7,200)
30	150	30	152	30	150 (delayed summit)
60	140	60	152	60	164
90	130	90	144	90	156

Graphically the record would appear in Chart 1

We can express the fact that the subject showed a delayed summit after doing 7,200 foot-pounds of work and did not show a delayed summit after 6,000 foot-pounds of work as in Chart 2

We have omitted any mention of the time in which the work is done Patients soon acquire a regular rhythm in working, the time of each swing being the same (2 to 3 seconds) Thus, the time factor becomes a constant and can be left out of consideration

The accompanying series of charts (Charts 3, 4, 5 and 6) shows the change in reactions of the blood pressure to muscular work during convalescence

It will be observed that all the convalescent patients show the same phenomenon—a progressive increase in the amount of work that can be done without causing a delayed summit of blood pressure This increase in all cases was synchronous with subjective symptoms of

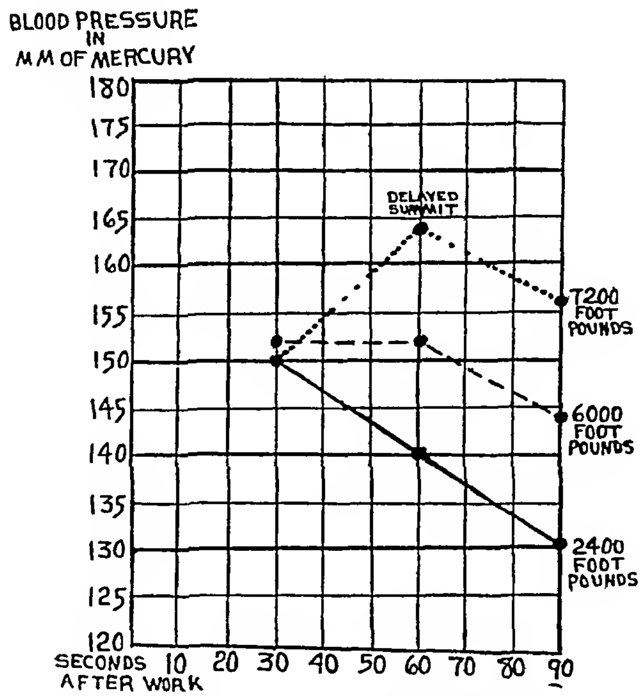

Chart 1—This chart shows a typical series of blood pressure readings after increasing amounts of work The subject was a normal man 26 years old Note that after a small amount of work the pressure falls rapidly, after a greater amount of work the return to normal is not so rapid, after a still greater amount of work the blood pressure continues to increase for some time—"delayed summit" The blood pressure before exercise was about 125

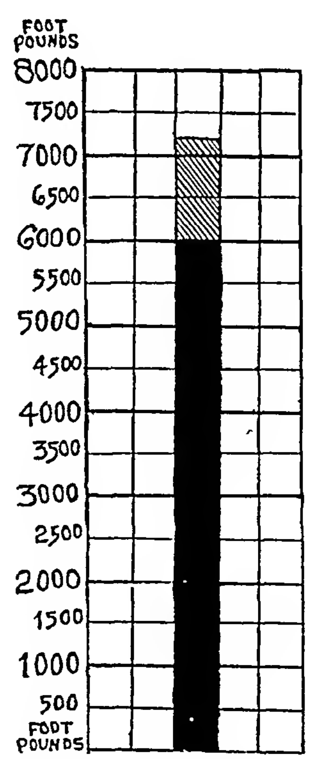

Chart 2—This chart indicates that with 6,000 foot-pounds of work or less there is no delayed summit, with 7,200 foot-pounds of work or more there is a delayed summit, between 6,000 and 7,200 foot-pounds the circulatory reaction to work changes

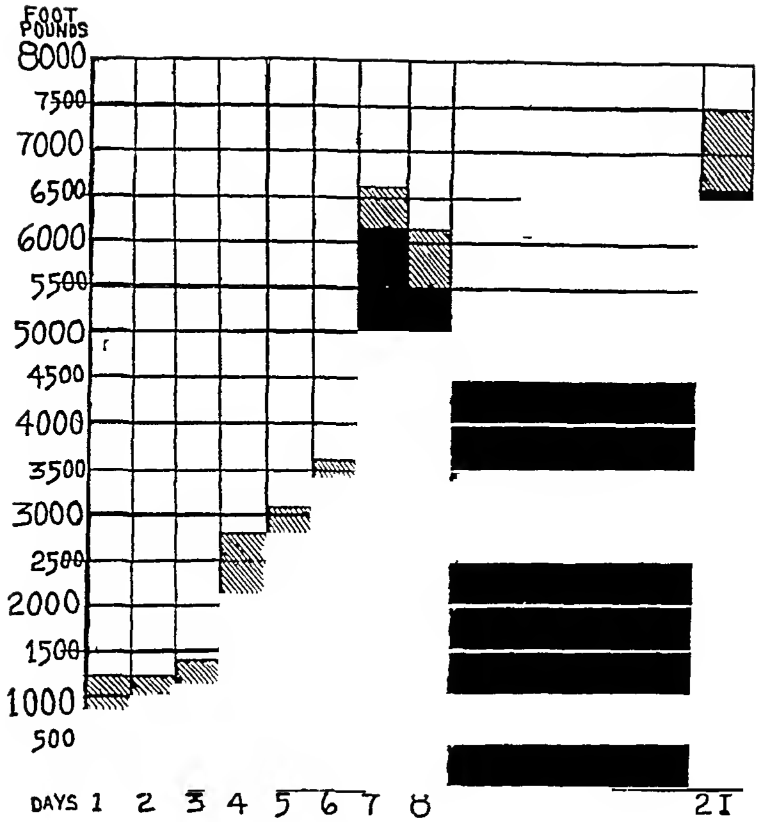

Chart 3

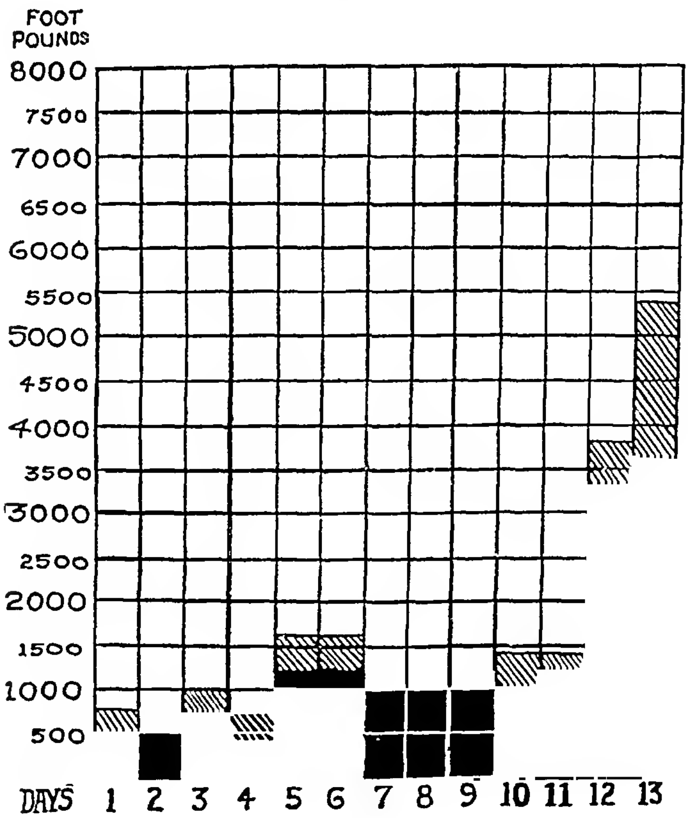

Chart 4

Charts 3 and 4—These charts show the change in the circulatory reaction to exercise which takes place during convalescence Chart 3 is from the patient I M in Table 1, Chart 4 is from the patient C B in Table 1

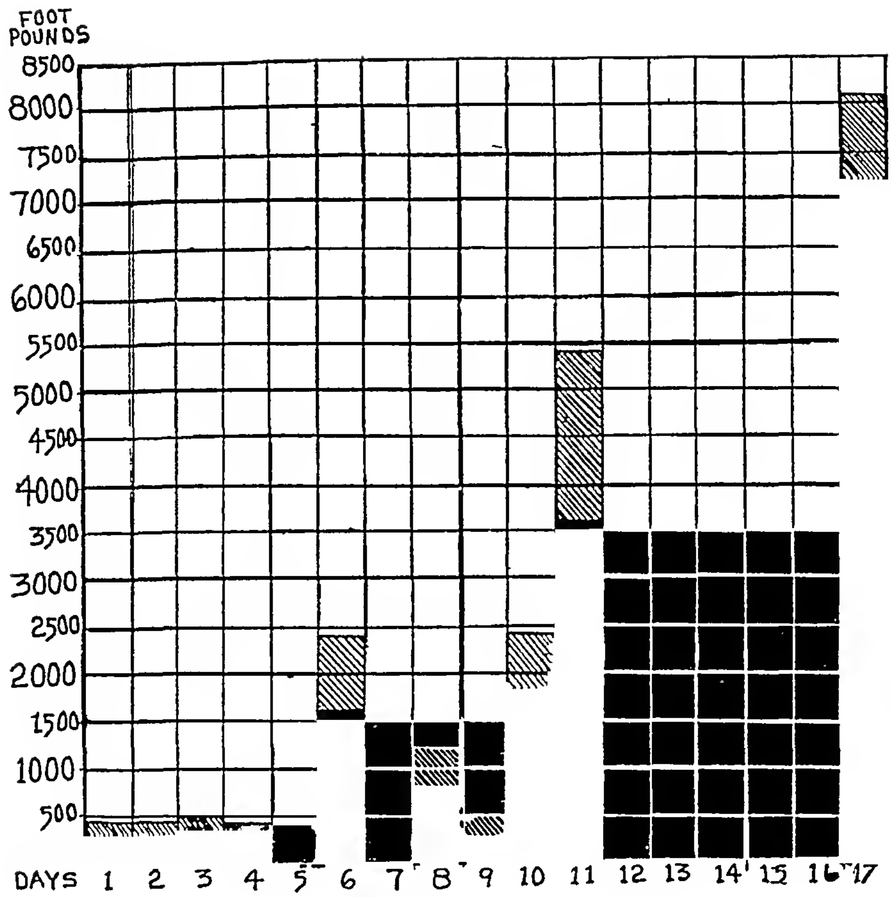

Chart 5

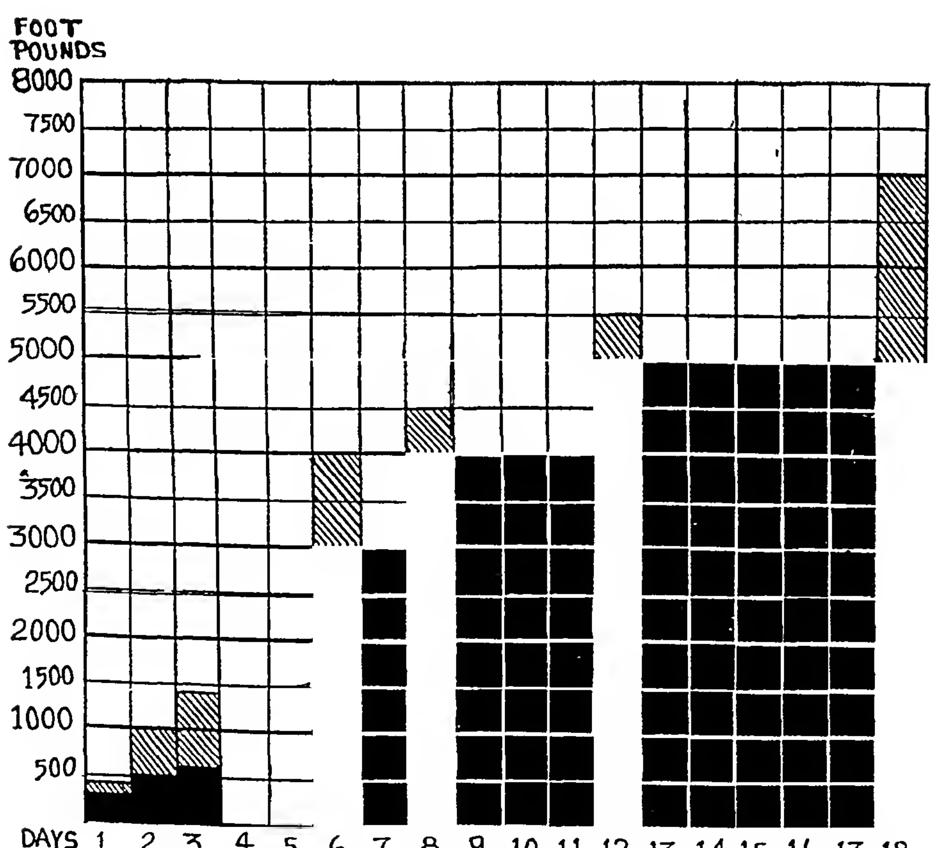

Chart 6

Charts 5 and 6—These are like charts 3 and 4 They show the same progressive change in circulatory reactions Chart 5 is from the patient R F in Table 1, Chart 6 is from the patient M O in Table 1

improvement and increased activity Patients R F and C B, who show a late development of this phenomenon, were subjectively weak and improved very slowly before the time at which the objective improvement in the circulatory reactions began Synchronously with the objective improvement there was marked subjective and clinical improvement

In the cases I M, C B, R F and M O, which were followed carefully with daily readings, it will be noted that this change in the circulatory reactions is most marked during a period of a very few days In the case of I M the change in four days was from 1,500 to 6,500 foot-pounds In the case of R F, in two days the point at which the delayed summit appeared rose from 500 to 5,000 foot-pounds C B rose from 1,500 to about 5,000 foot-pounds in two days M C changed from about 1,000 to above 3,000 in two days

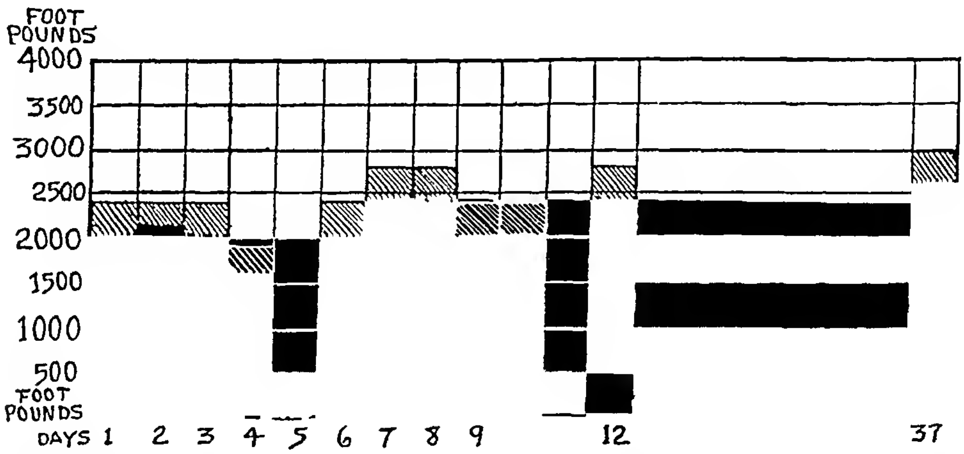

Chart 7—This chart shows the circulatory reactions to exercise in a normal woman taken day after day Note that the daily variation is comparatively slight Compare with Charts 3, 4, 5 and 6

That this change is not a mere result of the exercises to which the patient is subjected in the process of trying out his circulatory reactions is shown by the control Chart 7 The control was a normal woman not used to exercise Observe that there is no marked change produced by the amount of exercise necessary to try out her circulatory reactions

Table 1 summarizes our results in this series of patients

When the method of frequent readings is used we obtain a result something like that shown in Chart 8, which is taken from the case R F

Both the slow readings and the rapid readings are given, and it will be observed that they both give exactly the same conclusions as regards the circulatory reactions The readings taken at thirty, sixty and ninety seconds with the rapid method compare well with the same readings taken with the infrequent method We have observed this

TABLE 1—CHANGE IN REACTION OF THE SYSTOLIC PRESSURE TO EXERCISE DURING CONVALESCENCE *

Patient	Age	Disease	Recovery	Circulatory Reactions to Exercise Days									
I M	22	Lobar pneu monia	Crisis —9 days	1 1,200 900	2 1 200 1,000	3 1,400 1,120	4 2,800 2,100	5 3,060 2,800	6 3,600 3,420	7 6,600 6,160	8 6,160 5,500		21 7,500 6,600
C B	40	Lobar pneu monia	Crisis —6 days	1 750 500	3 1,000 750	4 750 400	5 1,600 1,200	6 1,600 1,200	10 1,400 1,000	11 1,400 1,200	12 3,800 3,300	13 5,400 3,000	
R F	41	Lobar pneu monia	Lysis —6 to —3 days	1 450 300	2 450 300	3 500 460	4 450 360	6 2,400 1,600	8 1,200 800	9 500 300	10 2,400 1,800	11 5,400 3,600	17 8,100 7,200
M O	23	Lobar pneu monia	Crisis —3 days	1 450 300	2 1,000 500	3 1,400 600	5 4,000 3,000	8 4,500 4,000	12 5,500 5,000				18 7,000 5,000
B M	44	Typhus	Crisis —9 days	1 1,300 1,100					6 2,500 2,100				
B B	27	Lobar pneu-monia	Crisis —12 days	1 2,300 1,800						7 3,500 3,000			
O G	22	Fibrinous pleurisy		1 200 0			4 2,200	5 3,500					
J O	21	Typhoid	Lysis —1 to +2 days	1 600	2 1,100 600			5 1,100				9 2,600 1,800	20 5,300
W M		Lobar pneu monia	Crisis —3 days	1 400 200						7 1,400 800		9 1,600 1,200	
H R	21	Lobar pneu monia	Crisis —15 days	1 1,900 1,500		3 4,000 3,200	4 5,000 4,000						

* The lower numeral of each pair gives the greatest amount of work, calculated in foot-pounds, which was not followed by a delayed summit The upper numeral gives the smallest amount of work which was followed by a delayed summit For example Patient I M was tested for the first time nine days after his crisis and showed a delayed summit with 1,200 or more foot-pounds of work, while with 900 foot-pounds or less he showed no delayed summit Twenty-one days later he showed a delayed summit with 7,500 foot-pounds of work or more and no delayed summit with 6,600 foot-pounds or less Note The patients, I M, C B, R F, and M O, have their reactions represented graphically in Charts 3, 4, 5 and 6, respectively

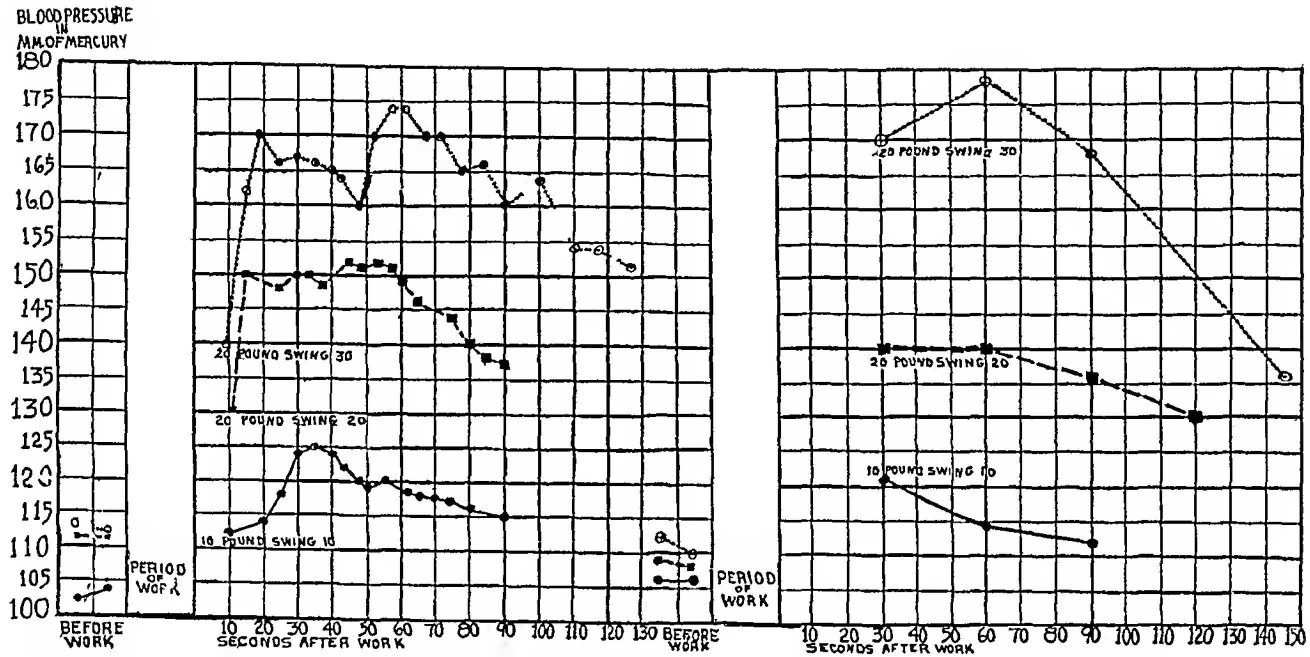

CHART VIII

Chart 8—This is a comparison of the frequent and infrequent methods of taking the systolic pressure after exercise Note that the readings taken at thirty, sixty and ninety seconds by both methods give curves which correspond very closely The work was all done on the same day and the patient rested from five to ten minutes after each exercise

same correspondence whenever we have compared the two methods The infrequent or slow method, while it does not give us such detailed information about the exact shape of the curve, does give us the information which we have found to be of the most value, that is, whether or not there is a delayed summit It is a method which is much easier to use, since it requires only one examiner, while, with the frequent reading method, two persons are required, one to read and one to record For practical work the Barringer method has the advantage of simplicity combined with adequacy

EFFECT OF EXERCISE ON THE PULSE RATE

Table 2 shows the pulse reactions to exercise of nine patients who were recovering from infectious diseases The presence or absence of a delayed summit of systolic pressure after exercise is also recorded for purposes of comparison It will be observed that the table shows thirty-two delayed summits, twelve of which show a delay in the return of the pulse to normal, while in the other twenty there is no such delay shown

In general, the rate increases with increased amounts of exercise and takes an increasingly longer time to return to normal with increased amounts of work, but this general rule has many exceptions, especially in patients who show a marked slowing after exercise, probably due to nervous influence on the heart rate

We have been able to make no deductions of value from the effects of work on the pulse rate or from the time required for the rate to return to normal after work in this small series of patients

The agreement of our objective circulatory findings with subjective and clinical changes in the patients whom we have examined has been very striking Our observations on different convalescent patients have shown a marked similarity and the results of these experiments afford evidence of considerable importance in support of the contention advanced by Barringer[1] that a delayed summit indicates an overtaxing of the cardiac reserve power

Any method which will permit of fairly accurate objective measurement of the stage of convalescence has abundant possibilities of development and of use, both in the immediate present and in the future It is most important at present that the convalescence of our soldiers be expedited as much as is consistent with good therapeutics For the maximum of efficiency in this direction some standard objective method of testing the soldier's ability to resume active service is of great importance Such a method these experiments seem to indicate

So far the method of testing the circulatory reactions to exercise has been applied only to patients convalescing from acute infections There is considerable probability of our getting useful information from the application of this method of study to patients who are recovering from the more chronic affections

TABLE 2—Effect of Work on the Pulse Rate of Patients During Convalescence*

Patient	Work	Pulse Rate		Return to Normal, Seconds	Delayed Summit	Delay, Seconds
		Before	Immediately After			
	Times					
M O	Sat up 5	68	86	180	No	
	Sat up 10	68	92	180	No	
	Sat up 15	80	88	120	No	
	7 lb swing 5	96	108	120	No	
	7 lb swing 10	88	108	120	No	
	10 lb swing 10	90	114	120	Yes	58
	7 lb swing 5	92	96	120	No	
	7 lb swing 10	88	104	120	No	
	10 lb swing 10	84	108	120	No	
	10 lb swing 15	84	112	120	No	
	20 lb swing 15	84	124	180	No	
	10 lb swing 5	96	108	180	No	
	10 lb swing 10	92	108	180	No	
	10 lb swing 10	92	112	120	No	
	10 lb swing 20	98	124	180	No	
	20 lb swing 20	96	144	180	Yes	60
	20 lb swing 10	104	128	120	No	
	20 lb swing 15	104	140	180	No	
	20 lb swing 25	104	158	180	Yes	60
	20 lb swing 35	104	156	240	Yes	60
W M	Sat up 5	58	60	60	No	
	Sat up 10	60	72	120	Yes	60
	10 lb swing 25	80	116	90	No	
	20 lb swing 20	84	132	120	Yes	60
	20 lb swing 15	90	112	118	No	
	20 lb swing 20	96	124	120	Yes	60
	20 lb swing 25	96	128	120	Yes	60
C B	20 lb flex 10	68	84	120	Yes	60
	20 lb flex 20	68	88	120	Yes	60
	10 lb flex 15	68	84	60	No	
	10 lb flex 20	72	80	120	No	
	10 lb flex 30	74	92	120	No	
	10 lb swing 10	72	100	120	No	
	10 lb swing 20	84	108	120	No	
	20 lb swing 20	72	132	240	No	
	20 lb swing 30	76	144	150	Yes	60
	20 lb flex 15	50	76	120	No	
	20 lb flex 20	54	72	90	Yes	60
	20 lb flex 30	54	76	120	Yes	60
R F	Sat up 10	76	82	120	No	
	Sat up 12	72	88	120	No	
	Sat up 15	72	88	120	Yes	61
	10 lb swing 10	64	88	120	No	
	20 lb swing 20	68	112	120	No	
	20 lb swing 30	68	128	240	Yes	55
	20 lb swing 30	88	120	150	No	
	20 lb swing 35	84	136	240	No	
	20 lb swing 40	84	140	300	No	
	20 lb swing 45	84	148	360	Yes	60

* The exercises in each group were given on the same day and five to ten minutes intervened between individual exercises The figure 120 in the column headed "Return to Normal" means that the rate became normal in two minutes or less

TABLE 2—EFFECT OF WORK ON THE PULSE RATE OF PATIENTS DURING CONVALESCENCE *—(*Continued*)

Patient	Work	Pulse Rate		Return to Normal, Seconds	Delayed Summit	Delay, Seconds
		Before	Immediately After			
	Times					
E W	Sat up 10	52	72	180	Yes	90
	Sat up 15	52	72	180	Yes	90
	Sat up 20	48	72	120	Yes	150
	Sat up 10	40	48	120	Yes	90
	Sat up 15	40	52	120	Yes	90
J O	7 lb flex 21	112	128	120	Yes	90
	7 lb flex 30	112	136	250	Yes	210
	7 lb swing 5	96	112	120	Yes	60
	7 lb swing 10	104	124	120	Yes	120
	10 lb swing 5	108	120	180	No	
	10 lb swing 5	96	112	120	No	
	10 lb swing 10	92	108	180	No	
	10 lb swing 15	100	120	120	No	
	10 lb swing 20	96	92	180	Yes	58
	10 lb swing 10	112	120	120	No	
	10 lb swing 15	112	124	120	No	
	10 lb swing 20	108	136	180	No	
	20 lb swing 20	112	156	300	No	
	20 lb swing 25	120	160	180	No	
	30 lb swing 20	116	168	300	No	
I F	10 lb swing 5	72	88	120	No	
	10 lb swing 10	72	104	180	No	
	10 lb swing 15	76	104	180	No	
	10 lb swing 20	88	88	300	Yes	120
J E	10 lb swing 10	76	88	120	No	
	20 lb swing 10	72	92	180	No	
	20 lb swing 15	80	108	120	Yes	60
	20 lb swing 15	72	92	120	No	
	20 lb swing 20	76	100	120	Yes	60
C G	10 lb flex 10	112	116	120	Yes	60
	10 lb flex 15	108	112	180	Yes	61
	10 lb flex 10	96	130	180	No	
	10 lb flex 15	104	104	180	No	
	10 lb flex 20	100	108	120	No	
	10 lb flex 25	104	104	180	No	
	15 lb flex 20	100	136	180	No	
	10 lb swing 10	112	116	120	No	
	10 lb swing 15	112	120	120	No	
	10 lb swing 10	104	116	120	No	
	10 lb swing 20	104	116	120	Yes	60

SUMMARY

1 The circulatory reactions of ten patients convalescing from acute infectious disease have been studied objectively

2 The pulse reactions have not given us any information of value

3 The blood pressure reactions have shown a progressive increase in the amount of work necessary to produce a "delayed summit" This increase has been shown in all cases, has been especially marked in a short period of a very few days, and has been synchronous with clinical and subjective improvement

CONCLUSION

The reaction of the systolic blood pressure to exercise in a convalescent patient affords valuable objective evidence of the stage of the patient's convalescence

I wish to express my indebtedness to Dr Alfred Meyer, Dr Emanuel Libman, and Dr Morris Manges for permission to follow the convalescence of patients on their wards

THE OCCURRENCE OF MITOCHONDRIA IN THE RED BLOOD CORPUSCLES DURING EXPERIMENTAL ANEMIAS *

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SAN FRANCISCO

INTRODUCTION

Mitochondria are small bodies of a lipoid nature which occur in the cell protoplasm and which may be stained in a specific manner by a variety of methods [1] They possess no fixed morphologic characteristics, but appear either as granules of varying size or as tiny rods They are said by some to be present in all nucleated cells

Mitochondria are not demonstrable in the circulating nonnucleated erythrocytes of healthy adult mammals Shipley[1] and others have shown, however, that they are regularly present in nucleated red cells In such cells they have been observed in the circulating blood of lower vertebrates, in the circulating blood of mammalian embryos and in the bone marrow of adult mammals Of more immediate interest is the fact that mitochondria have also been demonstrated in certain nonnucleated erythrocytes under conditions in which one would expect to find youthful cells of this type For example, nonnucleated red cells that contained mitochondria have been demonstrated in the bone marrow and circulating blood of mammalian embryos, in the bone marrow of normal mammalian adults and in the circulating blood of man during the course of some diseases in which the blood-forming organs are supposedly stimulated to increased activity Their presence in nonnucleated erythrocytes, therefore, appears to indicate that such erythrocytes are relatively immature

The present study was undertaken in order to test this hypothesis further Anemias were produced experimentally in rabbits by bleeding or by the injection of phenylhydrazin hydrochlorid Such measures lead to an increased activity on the part of the erythroblastic tissues and to the escape of more or less immature red cells into the circulating blood One might anticipate, therefore, that in such anemic animals mitochondriated red cells would appear in the circulating blood owing to the escape of immature forms from the bone marrow

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* Submitted for publication Feb 13, 1918

* From the Division of Medicine, Stanford Medical School

1 Cowdry, E V The Vital Staining of Mitochondria with Janus Green and Diethylsafranin in Human Blood Cells, Internat Monatschr f Anat u Physiol, 1914, **31,** 267, the General Functional Significance of Mitochondria, Am Jour Anat, 1916, **19,** 423 Shipley, P G The Mitochondrial Substance in the Erythrocytes of the Embryo Pig, Fol Haem, 1916, **20,** 61

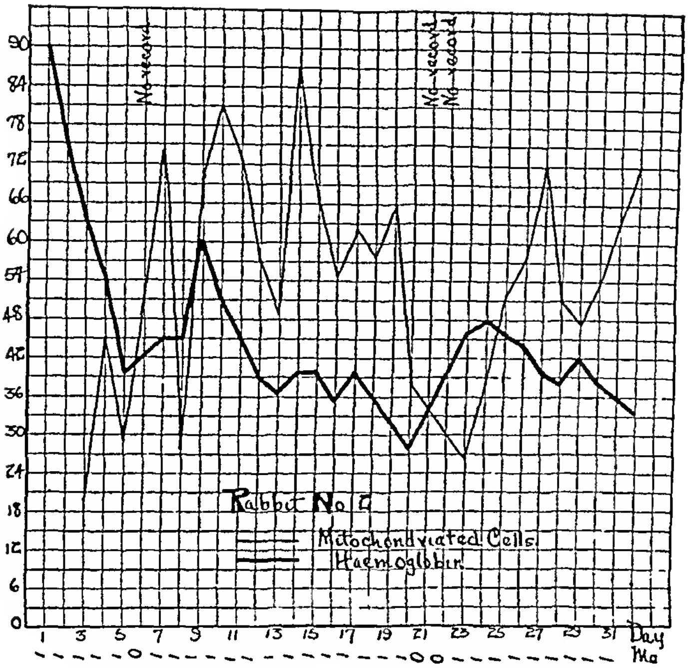

Chart 1—Rabbit 2 Injections as noted

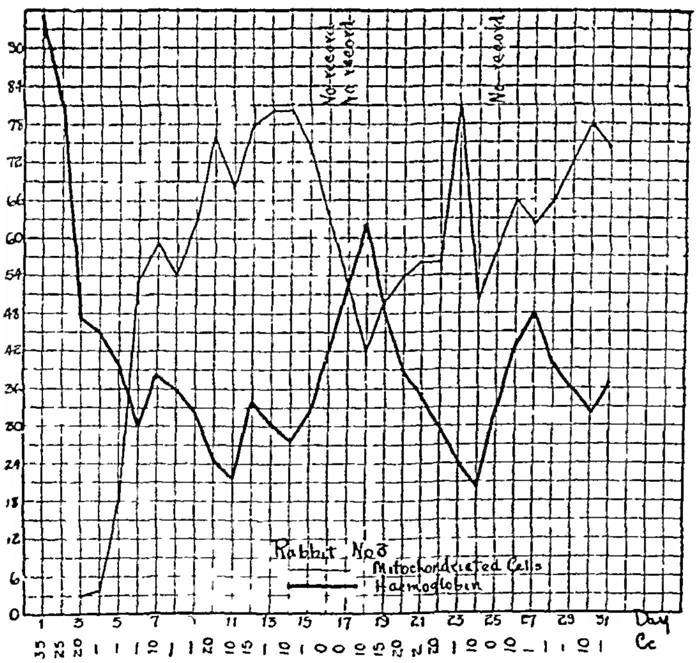

Chart 2—Rabbit 3—Injections as noted

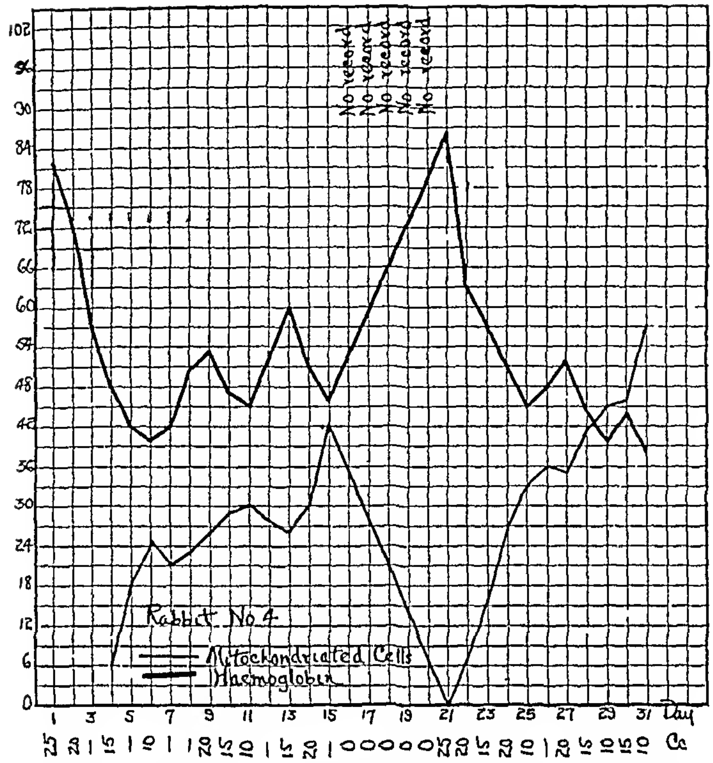

Chart 3—Rabbit 4 Bleeding as noted (—is ditto)

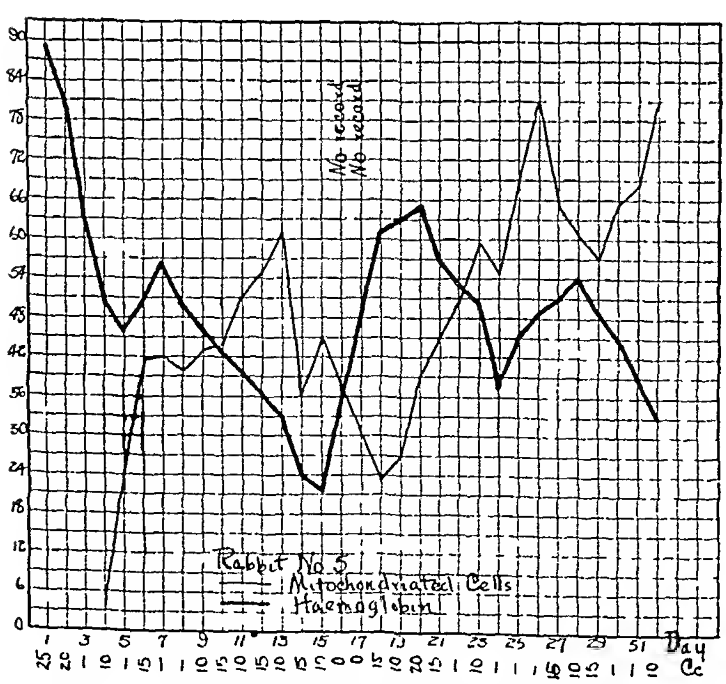

Chart 4—Rabbit 5 Bleeding as noted (— is ditto)

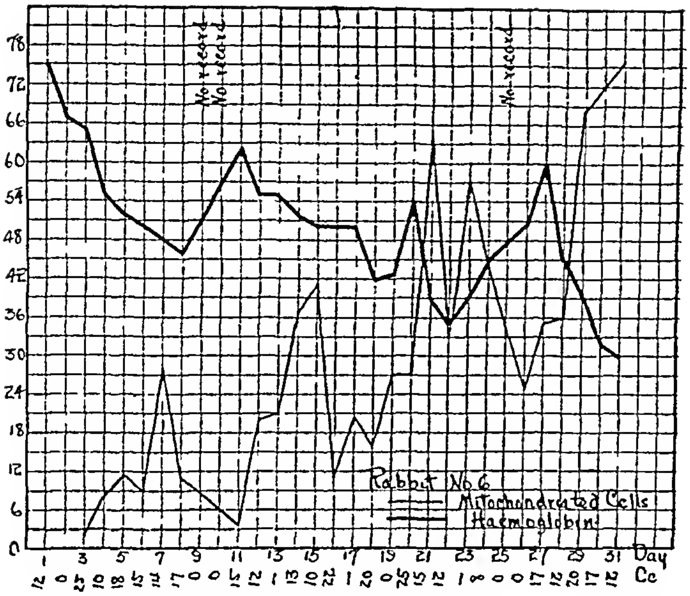

Chart 5—Rabbit 6 Bleeding as noted (— is ditto)

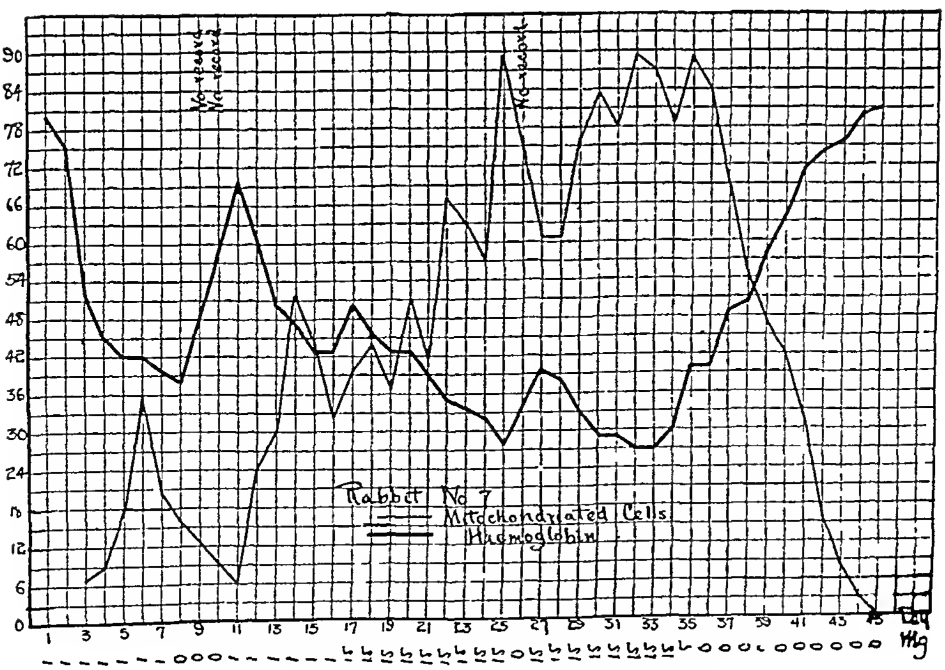

Chart 6—Rabbit 7 Injections as noted

Technic—As has been said, the rabbits used in this study were made anemic either by bleeding or by the injection of phenylhydrazin hydrochlorid When the former method was used, from 10 to 30 c c of blood were withdrawn daily, when the latter was used, from 1 to 1 5 mg of the the poison were injected daily In both cases, however, partial or complete recoveries were at times permitted by omitting the bleedings or the injections for one or more days during the experiments

The hemoglobin percentage was determined almost daily by the Sahli hemoglobinometer Smears stained by Wright's method were also examined in some of the experiments in order to compare the number of mitochondriated cells with such alterations in the red corpuscles as were demonstrable by this method

TABLE 1—Data of Experiments, Rabbit 2, Female, Weight 2 2 Kg

Day	Hemoglobin, Per Cent	Mitochondriated Cells	Pheynl hydrazin, Mg	Stained Smear
1	90	0	1	No change
2	76	0	1	No change
3	65	20	1	Many kernschatten, moderate amount of polychromatophilia
4	55	46	1	Slight anisocytosis and polychromatophilia, a rare normoblast
5	40	29	1	A few polychromes, very slight poikilocytosis, a rare normoblast
6	No record			No record
7	45	74	1	Slight polychromatophilia and basophilic degeneration, marked anisocytosis
8	45	28	1	Moderate amount of poikilocytosis, anisocytosis
9	60	70	1	Slight polychromatophilia
10	50	81	1	Cells large, no normoblasts
11	45	73	1	A few polychromes and basophils, no normoblasts
12	40	57	1	No other changes
13	37	49	1	Some polychromatophilia
14	40	87	1	No change
15	40	66	1	A few polychromes
16	35	55	1	Small amount of anisocytosis
17	40	62	1	A few polychromes
18	36	58	1	A few large cells
19	32	66	1	No normoblasts seen
20	28	38	1	Slight poikilocytosis
21	No record			No record
22	No record			No record
23	46	26	1	Polychromatophilia, a rare normoblast
24	48	40	1	Many large cells, some poikylocytosis
25	46	52	1	Some polychromatophilia
26	44	58	1	Some anisocytosis
27	40	72	1	Some basophilic cells, a few polychromes
28	38	51	1	Slight anisocytosis, many large cells
29	42	47	1	No other changes
30	38	53	1	No other changes
31	36	63	1	Slight polychromatophilia
32	34	72	1	No other changes

The following technic for staining mitochondria was used A stock solution of Janus Green B (Farbwerke-Hoechst Co, New York) was made in water in a concentration of 1 to 2,000 Before use this was mixed with a stock solution of sodium chlorid (1 08 per cent) in the proportion of one part of stain to two parts of the salt solution A drop each of blood and of the staining mixture were placed on a slide and immediately covered with a cover slip In such preparations mitochondria appeared as dancing granules or rods of a bright green color

To determine the proportion of mitochondria red blood cells preparations were placed under the oil immersion lens of a Leitz microscope (ocular 2) A 60 watt tungsten light with frosted globe furnished the illumination A number of evenly distributed fields in different parts of each preparation were selected, the total cells counted and the mitochondriated cells separately enumerated From these figures the percentage of the latter was computed In each set of preparations from 500 to 1,000 cells were counted

TABLE 2—Data of Experiments, Rabbit 3, Female, Weight 1 5 Kg

Day	Hemoglobin, Per Cent	Mitochondriated Cells	Blood Taken, C c	Stained Smear
1	95	0	21	No changes
2	80	0	25	Many kernschatten, a few polychromes
3	47	3	20	No visible changes
4	45	4	20	Marked anisocytosis and polychromatophilia, many large cells
5	40	18	20	Anisocytosis and polychromatophilia not so marked
6	30	53	20	No changes
7	38	59	10	Slight poikilocytosis, no other changes
8	36	54	15	Slight amount of basophilic stippling
9	32	62	15	Many large cells, many polychromes and basophils
10	25	76	20	Smear about the same
11	22	68	10	Some anisocytosis
12	34	78	15	A rare normoblast, some polychromatophilia
13	30	80	15	Slight poikilocytosis
14	28	80	10	A rare normoblast
15	32	74	10	Some polychromatophilia and anisocytosis
16	No record			No record
17	No record			No record
18	62	42	10	Slight poikilocytosis
19	47	50	15	Slight anisocytosis and polychromatophilia
20	39	54	20	Slight polychromatophilia
21	35	58	25	Slight basophilic degeneration
22	30	58	20	Much polychromatophilia
23	24	81	20	Some anisocytosis and polychromatophilia
24	20	50	10	A very rare normoblast, slight amount of polychromatophilia
25	No record			No record
26	43	66	10	Slight poikilocytosis
27	48	62	15	Slight anisocytosis
28	40	66	15	No changes
29	36	72	15	Slight polychromatophilia
30	32	78	10	No visible changes
31	40	74	10	Marked anisocytosis

TABLE 3—Data of Experiments, Rabbit 4, Female, Weight 2 4 Kg

Day	Hemoglobin, Per Cent	Mitochondriated Cells, Per Cent	Blood Taken, C c
1	82	0	25
2	72	0	20
3	62	0	20
4	48	5	15
5	42	18	15
6	40	25	10
7	42	21	10
8	50	23	10
9	53	26	20
10	47	29	15
11	45	30	10
12	52	28	10
13	58	26	15
14	52	30	20
15	46	42	20
16	No record		
17	No record		
18	No record		
19	No record		
20	No record		
21	88	0	25
22	64	7	20
23	56	16	15
24	53	23	20
25	46	33	10
26	48	36	10
27	52	35	20
28	44	41	15
29	40	45	10
30	44	46	15
31	38	57	10

TABLE 4—DATA OF EXPERIMENTS, RABBIT 5, FEMALE, WEIGHT 2 1 KG

Day	Hemoglobin, Per Cent	Mitochondriated Cells, Per Cent	Blood Taken, C c
1	89	0	25
2	79	0	20
3	62	0	20
4	50	4	10
5	46	23	10
6	50	41	15
7	56	42	15
8	50	40	15
9	46	43	10
10	43	45	15
11	40	51	10
12	37	55	15
13	33	61	10
14	25	36	15
15	22	45	10
16	No record		
17	No record		
18	61	23	15
19	63	27	10
20	65	39	20
21	57	45	15
22	53	50	15
23	50	59	10
24	38	55	10
25	45	69	10
26	49	81	10
27	51	65	15
28	54	59	10
29	49	55	15
30	45	65	15
31	39	68	15
32	33	81	10

TABLE 5—DATA OF EXPERIMENTS, RABBIT 6, FEMALE, WEIGHT 2 5 KG

Day	Hemoglobin, Per Cent	Mitochondriated Cells	Blood Taken, C c	Stained Smear
1	75	0	12 5	No changes noted
2	67	0	0	No changes
3	65	2	25	No changes noted
4	55	8	10	Many kernschatten, slight polychromatophilia
5	52	11	18	Marked anisocytosis
6	50	9	15	Marked anisocytosis
7	48	28	14	No change
8	46	11	17	No change
9	No record			No record
10	No record			No record
11	62	4	15	Some poikilocytosis and polychromatophilia
12	55	20	12 5	Many kernschatten
13	55	21	12 5	Some poikilocytosis and anisocytosis
14	52	37	13	Marked polychromatophilia, some poikilocytosis
15	50	41	10	Slight polychromatophilia, 8 normoblasts seen
16	50	11	22	Some anisocytosis and polychromatophilia
17	50	20	22	
18	42	16	20	
19	43	27	0	Many kernschatten, some anisocytosis
20	54	27	25	
21	39	64	15	Marked poikilocytosis, a few polychromes
22	35	33	12 5	
23	39	57	12 5	Same except for decrease in poikilocytosis
24	45	44	8	
25	No record			Marked polychromatophilia, some anisocytosis
26	50	25	0	
27	60	35	17	Slight polychromatophilia
28	45	36	12	
29	39	68	20	Some anisocytosis
30	32	72	17	
31	30	76	12	Slight polychromatophilia

TABLE 6—DATA OF EXPERIMENTS, RABBIT 7, FEMALE, WEIGHT 18 KG

Day	Hemoglobin, Per Cent	Mitochondriated Cells	Pheynl hydrazin, Mg	Stained Smear
1	80	0	1	No changes noted
2	75	0	1	No changes noted
3	52	7	1	No change
4	45	9	1	Slight anisocytosis and polychromatophilia
5	42	17	1	Some anisocytosis
6	42	36	1	Some polychromatophilia
7	40	20	1	Slight poikilocytosis
8	38	16	0	Some poikilocytosis, a few polychromes
9	No record			No record
10	No record			No record
11	70	6	1	Marked anisocytosis and poikilocytosis
12	60	24	1	Some polychromatophilia
13	50	30	1	Marked polychromatophilia
14	47	52	1	Slight polychromatophilia
15	43	44	1	Slight polychromatophilia
16	43	32	1	
17	50	40	1 5	Slight anisocytosis
18	46	44	1 5	
19	43	37	1 5	Slight poikilocytosis and polychromatophilia
20	43	51	1 5	
21	39	41	1 5	Slight polychromatophilia
22	35	67	1 5	
23	34	63	1 5	Marked number of polychromes
24	32	57	1 5	
25	28	89	1 5	Some polychromatophilia
26	No record			
27	40	61	1 5	Slight anisocytosis
28	38	60	1 5	
29	33	76	1 5	A few polychromes
30	29	83	1 5	
31	29	78	1 5	Slight anisocytosis and poikilocytosis
32	27	89	1 5	
33	37	89	1 5	
34	30	81	1 5	
35	40	91	1 5	
36	40	86	0	
37	49	71	0	
38	50	54	0	
39	58	47	0	
40	64	42	0	
41	73	24	0	
42	76	16	0	
43	78	8	0	
44	82	3	0	
45	83	0	0	

TABLE 7—DATA OF EXPERIMENTS, RABBIT 8, FEMALE, WEIGHT 19 KG

Day	Hemoglobin, Per Cent	Mitochondriated Cells, Per Cent	Phenylhydrazin, Cc
1	78	0	1 0
2	69	0	1 0
3	51	11	1 0
4	48	23	1 0
5	48	28	1 0
6	44	31	1 0
7	40	32	1 0
8	39	34	1 0
9	45	35	1 5
10	41	37	1 5
11	36	41	1 5
12	31	23	1 5
13	27	49	1 0
14	29	43	1 0
15	31	39	1 0
16	35	59	0
17	43	51	0
18	51	43	0
19	83	1	1 5
20	69	15	1 5
21	51	19	1 5
22	37	23	1 5
23	35	31	1 5
24	37	41	1 5
25	37	45	1 5
26	33	53	1 5
27	35	57	1 5
28	37	59	1 5
29	40	64	1 5
30	41	70	1 5
31	37	81	1 5

DISCUSSION

The details of the separate experiments can best be studied by referring to the accompanying tables and figures It will be noted that in none of the animals were mitochondriated red cells seen previous to the production of the anemia and that in each animal these cells occurred after its production, rising in several instances to a maximum of over 80 per cent of the total number of erythrocytes By reference to the figures it is also evident that in a general way the percentage of hemoglobin and the proportion of mitochondriated red cells varied in

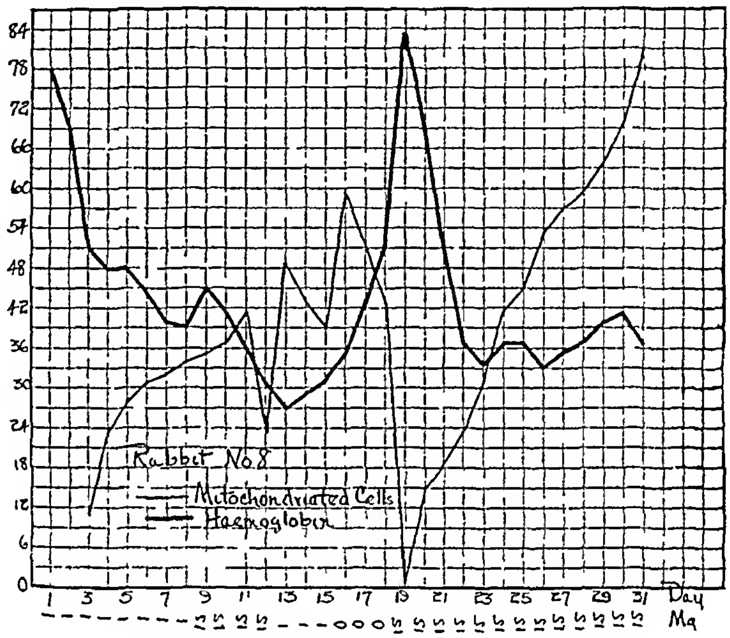

Chart 7—Rabbit 8—Injections as noted

the inverse direction In one instance (Rabbit 7) in which the hemoglobin was permitted to return to the normal, the mitochondriated cells gradually disappeared

TABLE 8—AVERAGE PERCENTAGE OF MITOCHONDRIATED CELLS AT DIFFERENT LEVELS OF HEMOGLOBIN

Number of Observations	Hemoglobin, Per Cent	Average Per Cent of Mitochondriated Cells	Per Cent Range of Variation
12	60-65	27	35
9	55-59	30	19
29	50-54	33	38
33	45-49	40	38
37	40-44	48	37
32	35-39	52	33
19	30-34	65	29
13	25-29	69	26

The inverse relation between the proportion of mitochondriated cells and the percentage of hemoglobin could also be demonstrated in

another way In Table 8 the average percentage of mitochondriated cells at different levels of hemoglobin is given These averages were compiled from all the counts made, irrespective of whether the hemoglobin was decreased by bleeding or by the injection of phenylhydrazin

No difference was noted in the relation between the percentage of mitochondriated cells and the hemoglobin concentration in the two different forms of anemia The mitochondria in the phenylhydrazin anemia, however, were more deeply stained and larger

Special attention was paid in certain experiments to the appearance of nucleated red cells and of polychromatophilic cells in smears stained by Wright's method The occurrence of these cells was subject to considerable variation and no constant relation could be established between the finding of nucleated red cells, the degree of polychromatophilia and the percentage of mitochondria-containing cells

CONCLUSIONS

If the presence of mitochondria in red blood cells is an indication that they are newly formed cells, one would expect to find an increase in their number whenever there is an increased rate of red cell formation The need for increased formation may be produced experimentally by the removal of blood or by the injection of phenylhydrazin hydrochlorid

The present study showed that these procedures were, in fact, accompanied by an increase in the number of mitochondria-containing red cells, and further that the degree of this increase was in the individual case roughly proportional, and on the average exactly proportional, to the need for red cells as measured by the degree of anemia produced

These experiments, therefore, support the suggestion that the number of red cells containing mitochondria may prove to be a useful indication of the rate of red blood cell formation in clinical and experimental conditions

The author wishes to acknowledge his indebtedness to Dr Thomas Addis for suggestions and aid during the course of this investigation

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RENAL GLYCOSURIA *

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MINNEAPOLIS

So-called renal diabetes has been reported at various times in the literature The term is now recognized as a misnomer and the condition should be called renal glycosuria True cases of renal glycosuria are rare and many so diagnosed are open to question, being mild or atypical diabetes mellitus

The lesion is apparently renal and due to a constant excretion by the kidney of a small amount of sugar while the blood sugar is normal The tissues can still utilize carbohydrates, and as a result on any diet the percentage of sugar excreted does not vary to any great extent The glycosuria is usually found by accident or routine examination, the patient reporting for life insurance or irrelevant illness Most of the patients do not present any of the clinical symptoms of diabetes mellitus and are apparently in good health Pathologically, the glycosuria seems to be due to a lowered kidney threshold for carbohydrates

The first essential necessary for a diagnosis is a blood sugar running within normal limits The level is placed differently by various authorities The general opinion at present places the normal percentage of blood sugar between 0 7 and 0 15 In this we concur In order to make the diagnosis of renal glycosuria, it is necessary to have the following data

1 A urine containing dextrose in amount unchanged to any great extent by fluctuation of carbohydrate intake

2 A blood sugar of normal percentage

A number of men have recorded cases of renal glycosuria Allen[1] has thoroughly reviewed the literature and asserts that he was able to find only two true cases of this condition, namely, those reported by Boringer[2] and Tachau [3]

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*From the Chemical Laboratory, Department of Medicine, University of Minnesota

1 Allen Glycosuria and Diabetes Boston, 1910, **1,** 544
2 Bonninger Deutsch med Wchnschr, 1908, **34,** 780
3 Tachau Deutsch Arch f klin Med, 1911, **104,** 448

Allen also says that other men have reported this condition when the correct diagnosis has been mild or atypical diabetes mellitus Such instances are recorded by Frank,[4] Roger and Chalin[5] and Salmon[6] Calambos[7] cites a case suggesting a phloridzin glycosuria Since Allen's review Graham,[8] De Langen,[9] Mosenthal and Lewis[10] have reported cases of renal glycosuria which seem to stand the test During the last few months, Murlin and Niles[11] have reported another case Because of the rarity of this disease and because of recent reports of Murlin and Craver[12] and Underhill[13] on decreased glycosuria after a sodium bicarbonate administration, this case is reported

REPORT OF CASE

History—E L, University Hospital, No 10625, woman, white, aged 21, born in Minnesota and descended from Swedish ancestry

Family History—Father (aged 48), mother (aged 50), one brother (aged 17) and one sister (aged 24) are living and well, one brother died in infancy, cause unknown, no tuberculosis, cancer, cardiac, or kidney disease in the immediate family, no history of obesity or diabetes mellitus Other members of the family have had their urines examined at various times and they have been found negative for sugar

Occupational History—During the six months prior to examination the patient was a clerk in a confectionery store The work was light and the hours not long She was previously a seamstress The needlework was very confining

Personal History—The patient had measles and whooping cough when a child, she was vaccinated and also had an appendectomy two years prior to admission The venereal history was negative to indirect questioning She had occasional frontal headaches during the previous few years, attributed to needlework The cardiorespiratory history was negative The gastro-intestinal history was negative up to the present illness, except for some nausea, with the headaches mentioned The genito-urinary history was negative to the present illness D 4-5/N-U Catamenia, normal The skin was always a little dry There was no loss of hair The highest weight was 130 pounds, two months prior to examination At the time of the examination it was 120 pounds Two years previously it was 107 pounds The patient sleeps well, uses no alcohol or drugs, but tea and coffee in moderation

Present Illness—For an indefinite period of two or three years the patient had noticed slight polyuria Nocturia was not present and no other urinary symptoms were noted

Two years prior to admission her physician removed the appendix, which was in a state of chronic inflammation There were never any acute symptoms and aside from slight tenderness over McBurney's point she had felt well Ether anesthesia was used On returning home after a normal convalescence of twelve

4 Frank Arch f exper Path u Pharmakol 1910, **72,** Nos 3 and 7
5 Roger and Chalin Arch d mal d l'apparat digest, 1912, **6,** 661
6 Salmon Deutsch med Wchnschr, 1914, **40,** 217
7 Calambos Deutsch med Wchnschr, 1914, **46,** 1301
8 Graham Jour Physiol, 1915, **49,** 46 (Proceedings)
9 De Langen Berl klin Wchnschr, 1914, **51,** 1792
10 Mosenthal and Lewis Bull Johns Hopkins Hosp, 1916, **27,** 134
11 Murlin and Niles Am Jour Med Sc, 1917, **153,** 79
12 Murlin and Craver Jour Biol Chem, 1916, **28,** 289
13 Underhill Jour Am Med Assn, 1917, **68,** 497

days, the patient was informed that sugar was present in her urine It had been found constantly during her stay in the hospital Since that time she had been under a physician's care There had never been any polyphagia or polydipsia Her diet and appetite were "equal to that of her friends and relatives" She gained in weight and considered herself well

During her second admission (six weeks in a hospital), her physician limited her diet Although a modified Allen diet was used, on only one day was she free of glycosuria Her blood sugar was never determined At the end of this time she was discharged from the hospital with instructions to limit the diet to 5 per cent and 10 per cent vegetables, with a normal protein and fat intake After that time, for a period of two years, glycosuria was present on each examination She gained in weight and height during this time and had always felt in normal health

There had been no change in the polyuria Polydipsia and polyphagia never developed She followed the prescribed diet strictly No symptoms of acidosis were present during this time The headaches mentioned disappeared after wearing glasses While a clerk in the confectionery store there had been no inclination to eat candy She said that during this period she had not "tasted candy over two or three times"

The patient was admitted to the hospital for study and for a further attempt to eliminate the glycosuria

Physical Examination—Temperature, 99 1 F , pulse, 100, respirations, 20, height, 5 feet, 1 5 inches, weight, 123 pounds A well developed and well nourished young woman lying in bed in no apparent discomfort, skin dry and slightly roughened over the entire body, hair wavy and present in normal amount, no deformities, and body of normal contour, no abnormal bony development noted, mucous membranes of good color and not pigmented, pupils equal and regular, reacting normally to light and accommodation, sclerae clear, no signs of exophthalmic goiter, ears negative for discharge and tophi, hearing good, mouth, tongue and pharynx normal, teeth and gums in good condition, tonsils negative, uvula bicornate, thyroid gland not palpable, axillary and inguinal glands palpable, pea to bean size

The lungs were normal, apical fields measured 5 cm and diaphragmatic excursion 4 cm , no abnormalities in breath sounds

Heart The apex could not be seen or felt, nipple was 10 5 cm to the left of the midsternal line, relative cardiac dulness measured 11 cm on the left and shifted 2 cm , upper dulness at the third rib and supracardiac dulness were normal The heart sounds were normal in time and rhythm No murmurs were heard and the pulmonic second sound was greater than the aortic second, pulse regular in force and rhythm and of good volume and tension

Abdomen There was a suprapubic scar 8 cm long The abdomen was soft normal in contour, and tympanitic, no masses or tenderness demonstrated Liver dulness appeared at the fourth rib and was lost at the costal margin The edge was not palpable The spleen and kidneys were not felt

The extremities were negative, patellar reflexes present on reinforcement, Oppenheim and Babinski negative, no edema or thickening of the tibiae present

Rectal and vaginal examination were not indicated

Laboratory Data—The blood showed a normal red and white count, hemoglobin and differential, systolic blood pressure, 115 and diastolic, 78 mm of mercury, Wassermann reaction negative The phenolsulphonephthalein test showed 55 per cent excretion at the end of the first hour, 12 per cent at the end of the second hour, total 67 per cent Ambard's constant ranged from 0 08 to 0 09 The urine was clear, straw colored, and acid in reaction There was no albumin Traces of acetone and diacetic acid were present The microscopic examination was negative except for a few epithelial cells Benedict's and the fermentation tests were positive for sugar The phenylhydrazin test gave dextrose osazone crystals

The roentgenogram of the skull was negative and the sella normal in size and outline

Laboratory methods used Urinary nitrogen, Kjeldahl method, urinary ammonia, Rouchese-Malfatti,[14] urinary sugar, Benedict's solution, polariscope, urinary acetone, Lugol's solution, urinary diacetic acid, Gerhard's solution, alveolar carbon dioxid, collection with Plesch apparatus,[15] determined by Haldane apparatus,[16] alkaline reserve, Van Slyke apparatus,[17] pH of blood, Levy, Rowntree and Marriott,[18] chlorids of urine, Volhard-Harvey method,[19] blood sugar, Myers and Fine[20]

DISCUSSION

On admission, the case was thought to be one of atypical diabetes and the usual routine treatment was given in preparation for starvation, namely, the fats were first eliminated from the diet After four days' starvation, glycosuria was still present and the blood sugar remained at the same level as on admission In mild diabetes the glycosuria would usually have disappeared with such a glycemia A low caloric diet was next administered and starvation was later repeated The glycosuria still persisted and the blood remained unchanged to any great extent On account of this fact the dextrose-nitrogen ratio was determined After a constant diet of protein and fat for six days, the glycosuria disappeared The next few days, on starvation, glycosuria was absent, this being the only time during her stay in the hospital that the patient was sugar-free It was thought the case might correspond to the usual diabetic treatment, but on a diet containing 7 gm of carbohydrate the sugar output was 7 gm The blood sugar still remained fairly constant Our provisional diagnosis of renal glycosuria now seemed to be confirmed, and during the remainder of her stay in the hospital the patient was treated for this condition

Table 1 presents a metabolic study and shows, in addition, data relating to acid-base equilibrium The urine shows constantly a small amount of diacetic acid and acetone The urinary ammonia is usually within normal limits, but increased somewhat during the period of study of the dextrose-nitrogen ratio The alveolar carbon dioxid and alkaline reserve values were only slightly changed In the early part of the patient's stay the studies revealed a very mild acidosis, although no symptoms were present The pH of the blood on admission shows a mild grade of acidosis, and later is within normal limits

The remainder of the data relates to glycosuria and sodium bicarbonate and sodium chlorid intake Chart 1 is a graphic record of these

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14 Folin Laboratory Manual of Biological Chemistry, Appleton & Co, 1916

15 Plesch Ztschr f exper Path u Therap, 1909, **6,** 380

16 Haldane and Priestley Jour Physiol, 1905, **32,** 225

17 Van Slyke Proc Soc Exper Biol and Med, 1915, **12,** 165

18 Levy, Rowntree and Marriott The Archives Int Med, 1915, **12,** 389

19 Harvey The Archives Int Med, 1910, **6,** 12

20 Myers and Fine Chemical Composition of the Blood in Health and Disease 1915

studies Section 1 of the chart shows the period of starvation on a high salt intake During this period we were attempting to get the patient sugar-free The upper curves record the glycosuria and weight of the patient The midle curves record the chlorid intake and output The lower curves show the fluid balance

It will be noted that the patient lost 10 pounds in weight The

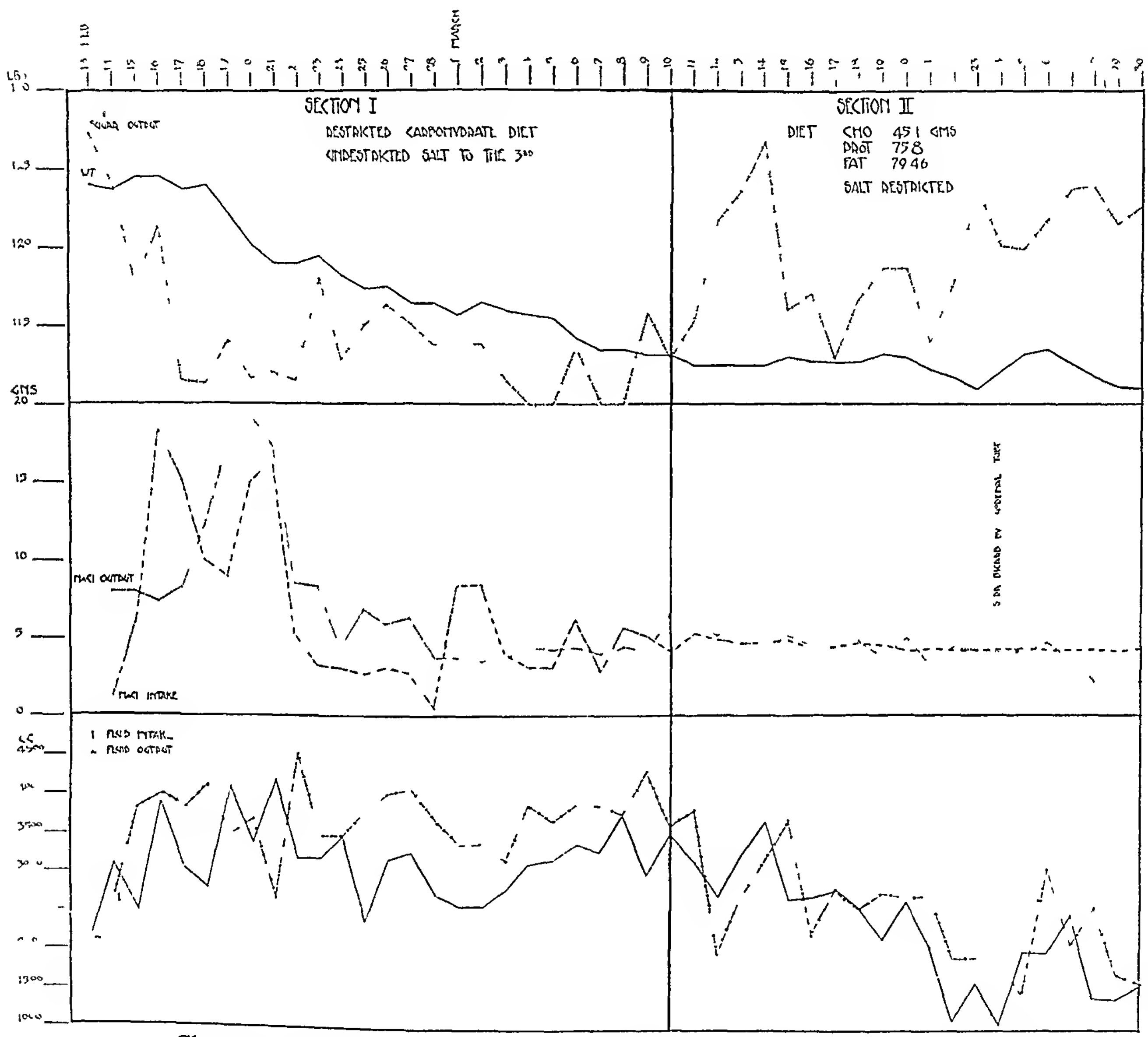

Chart 1—Upper curves record glycosuria and weight of the patient, the middle curves show the chlorid intake and output, the lower curves show the fluid balance, as explained more fully in the text

sugar excretion was lowest during the period of high salt ingestion The fluid curve does not show anything normal

Section 2 records the same curves after the diagnosis of renal glycosuria was established The patient was placed on a constant diet of carbohydrate, protein and fat for a period of two weeks The salt was restricted as much as possible, only the chlorids normally present

TABLE 1—DATA OF—

Date, Feb 1917	Fluid Intake in C c	Amount Urine in C c A M Spec	Specific Gravity	Reaction	Acid		Albumin	Sediment	D N Ratio	NH_3 Gm	Van Slyke	P H	CO_2 Tension in Mm Hg	Sod Bic
					A	D								
13		180	1 035	Ac	++	+++	0	0		0 37	37 50	7 30	38 79	0
13 14		2,200	1 010	Ac	++	+	0	cr -cts		1 25			38 79	0
14 15	2,745	3,100	1 007	Ac	+	0	0	0		1 21			41 78	0
15-16	3,843	2,500	1 007	Ac	+	0	0	0		0 90			37 30	0
16 17	4,000	3,900	1 008	Ac	++	++	0	0		1 05	35 93		41 78	0
17 18	3,840	3,050	1 006	Ac	++	++	0	0		0 73			38 09	0
18 19	4,125	2,800	1 008	Ac	+	++	0	0		0 84				0
19 20	3,500	4,100	1 007	Ac	+	+	0	0		1 19			49 09	0
20-21	3,700	3,400	1 012	Ac	+	+	0	0		2 07				0
21 22	2,700	4,200	1 007	Ac	+	+	0	0		1 34			35 90	0
22 23	4,500	3,200	1 009	Ac	+	+	0	0		2 14				0
23-24	3,500	3,200	1 010	Ac	+	+	0	0		1 57	34 50	7 35	37 30	0
24 25	3,500	3,500	1 005	Ac	+	+	0	0		1 99			38 09	0
25-26	3,800	2,400	1 010	Ac	+	+	0	0	1 09	1 37				0
26 27	4,040	3,200	1 007	Ac	+	+	0	0	1 30	2 33			35 81	0
27 28	4,100	3,300	1 005	Ac	+	+	0	0	0 72	2 24	36 08		26 81	0
28- 1	3,700	2,750	1 008	Ac	+	Tr	0	0	0 53	2 20			35 71	0
1 2	3,400	2,600	1 008	Ac	+	+	0	0	0 51	2 13	30 53		35 81	0
2 3	3,400	2,600	1 006	Ac	+	+	0	0	0 58	2 57			32 81	0
3 4	3,200	2,800	1 002	Ac	Tr	Tr	0	0	0 15	2 07			38 79	0
4 5	3,900	3,150	1 004	Ac	+	+	0	0	0	2 61				0
5 6	3,700	3,200	1 003	Ac	+	+	0	0	0	1 76			37 30	0
6- 7	3,900	3,400	1 004	Ac	+	+	0	0	0	2 03	34 77	7 35	35 06	0
7 8	3,900	3,300	1 005	Alk	+	+	0	0		?			36 55	0
8 9	3,800	3,800	1 004	Ac.	+	+	0	0		3 15				0
9 10	4,350	3,000	1 005	Ac	+	+	0	0		1 71			38 09	0
10-11	3,650	3,550	1 004	Ac	++	+	0	0		2 41			35 06	0
11 12	3,850	3,200	1 005	Ac	+	+	0	0		2 72				0
12 13	2,005	2,750	1 008	Ac	+	+	0	0		1 76			37 30	0
13 14	2,745	3,270	1 008	Ac	Tr	+	0	0		1 53	35 39	7 35	34 36	1 33
14 15	3,220	3,700	1 009	Ac	+	+	0	0		1 35			42 52	2 66
15-16	3,738	2,700	1 008	Ac	Tr	Tr	0	0			44 50	7 45	40 28	9 33
16 17	2,260	2,720	1 008	Alk	Sl tr	Tr	0	0		?			44 01	9 33
17 18	2,838	2,825	1 009	Alk	Tr	+	0	0		?			40 28	5 0

* B = Benedict, S = Saccharometer

—Metabolism Study of E L

Sugar* Excretion, per Cent Reduction		Total Sugar Excretion, Gm	General Diet			Alc in C c	Caloric Intake	Cal per Kg Body Weight	Wt, Kg	C H Bal	Blood Sugar per Cent	Blood Pressure	Pulse
D	S		C H Intake, Gm	Protein Intake, Gm	Fat Intake, Gm								
3 32	—	5 97				0	0	0	56 7		0 128		94
1 57	1 2	34 54				0	0	0	56 3				100
0 91	0 9	28 21	99 89	26 72	23 04	0	713 8	12 7	56 1	+71 68			102
0 62	0 6	15 50	34 12	15 93	23 15	0	408 5	7 23	56 5	+18 62		113—78	94
0 59	0 0	23 01	14 79	7 90	6 14	0	146 0	2 58	56 5	—8 22	0 126		80
—	0 1	3 05	0	0	0	0	0	0	56 1	—3 05			80
—	0 1	—2 80	0	0	0	0	0	0	56 3	—2 08			80
—	0 2	—8 20	0	0	0	0	0	0	55 5	—4 1			88
—	0 1	—3 40	0	0	0	0	0	0	54 6	—3 4	0 111		82
—	0 1	—4 20	10 64	12 08	15 57	0	234 6	4 3	54 0	—4 2			72
—	0 1	—3 20	10 64	12 08	15 97	0	234 6	4 3	54 0	—3 2			88
0 5	0 3	16 06	0	0	0	0	0	0	54 2	—16 06	0 119		80
0 17	0 1	5 88	0	0	0	0	0	0	53 6	—5 88			80
0 42	0 3	10 08	0	31 90	32 82	0	422 98	7 9	53 3	—10 08			76
0 40	0 3	12 89	0	45 50	49 24	0	625 16	9 5	53 3	—12 89			82
0 82	0 2	10 43	0	38 55	43 07	0	525 83	9 9	52 9	—10 43	0 108	96—68	66
0 28	0 2	7 70	0	45 50	49 24	0	625 16	11 8	52 9	—7 70			70
0 30	—	7 80	0	35 65	47 36	0	568 84	10 8	52 6	—7 80	0 111		72
0 30	0 29	7 93	0	35 65	47 36	0	568 84	10 7	52 9	—7 93			76
0 11	—	3 22	0	17 40	32 44	0	291 96	5 54	52 7	—3 22			80
0	0	0	0	0	0	0	0	0	52 3	0			73
0	0	0	0	0	0	0	0	0	52 4	0			82
0 21	0 2	7 14	7 09	14 35	14 84	0	219 32	4 23	51 8	0 05	0 111		66
0	0	0	5 18	10 99	17 45	0	221 73	4 30	51 5	+5 18		100—80	84
0	0	0	7 09	14 35	14 84	0	219 32	4 26	51 5	+7 09			80
0 39	—	11 82	11 13	19 11	24 59	0	343 27	6 67	51.3	0 69	0 097		76
0 16	0 2	5 85	0	33 96	13 48	0	155 28	3 02	51 4	—5 85			78
0 34	0 3	10 91	14 06	43 57	65 03	0	818 19	16 01	51 1	+3 15			76
0 84	—	23 10	45 10	75 80	79 46	0	1,198 74	23 4	51 1	+22 00			76
0 83	—	27 14	45 10	75 80	79 46	0	1,198 74	23 4	51 1	+17 96	0 144		68
0 90	0 9	33 44	45 10	75 80	79 46	0	1,198 74	23 4	51 1	+11 66			84
0 45	—	12 15	45 10	75 80	79 46	0	1,198 74	23 3	51 3	+32 95	0 124		90
0 52	—	14 14	45 10	75 80	79 46	0	1,198 74	23 4	51 1	+30 90			64
0 20	—	5 84	45 10	75 80	79 46	0	1,198 74	23 4	51 1	+39 20			84

TABLE 1—DATA OF METABOLISM—

Date, Feb 1917	Fluid Intake in C c	Amount Urine in C c A M Spec	Specific Gravity	Reaction	Acid		Albumin	Sediment	D N Ratio	NH3 Gm	Van Slyke	P H	CO2 Tension in Mm Hg	Sod Bic
					A	D								
18-19	2,603	2,600	1 014	Alk	Tr	Tr	0	0		?				8 0
19 20	2,798	2,200	1 014	Alk	Tr	Tr	0	0		?	41 88	7 45	41 78	8 0
20-21	2,748	2,700	1 010	Alk	0	Tr	0	0		?			38 09	0
21-22	2,763	2,100	1 011	Ac	0	Tr	0	0		1 11				0
22 23	1,988	1,150	1 017	Alk	++	+	0	0		?			41 03	0
23-24	1 990	1,643	1 013	Ac	+	+	0	0		1 20	42 57		41 03	0
24 25	1,963	1,100	1 025	Alk	+	+	0	0		?			37 30	5 0
25-26	1,413	2,050	1 012	Alk	+	+	0	0		?				5 0
26-27	3,138	2,040	1 016	Heat	+	+	0	0		?	35 81 41 74		41 78	5 0
27-28	2,150	2,546	1 011	Alk	+	+	0	0		?			41 03	0
28-29	2,598	1,458	1 018	Ac	+	+	0	0		0 641			36 33	0
29 30	1,848	1,440	1 016	Ac	+	+	0	0		1 076			38 79	0
30-31	1,653	1,612	1 017	Alk	+	+	0	0		0 275	37 32	7 45	37 76	0
31- 1	Disch	arged												

TABLE 2—SUGAR—

Date	Type of Diet	Fluid	6-8 a m		8-10 a m		10-12 a m	
			Urine, C c	Sugar, Gm	Urine, C c	Sugar, Gm	Urine, C c	Sugar, Gm
23-24	Restricted salt	Urine	58	1 04	325	2 92	315	1 94
		Blood						0 122%
26-27	Restricted salt, soda bicarb by duodenal tube	Urine	120	0 848	118	0 778	332	2 22
		Blood		0 136%				
27-28	Restricted salt, soda bicarb by duodenal tube	Urine	462	1 52	108	1 94	185	2 40
28-29	Restricted salt, soda bicarb dis continued	Urine	79	1 68	276	4 00	134	3 21
29-30	Restricted salt	Urine	100	2 29	256	2 89	208	3 07
30-31	Restricted salt	Urine	88	1 76	292	1 63	200	1 70
		Blood						0 13%
31-1	Restricted salt	Blood						0 144%

Diet Carbohydrates, 45 1 gm, proteins, 75 8 gm, Fats, 79 46 gm

—Study of E L—(*Continued*)

Sugar* Excretion, per Cent Reduction		Total Sugar Excretion, Gm	General Diet			Alc in C c	Caloric Intake	Cal per Kg Body Weight	Wt, Kg	C H Bal	Blood Sugar per Cent	Blood Pressure	Pulse
D	S		C H Intake, Gm	Protein Intake, Gm	Fat Intake, Gm								
0 51	—	13 31	45 10	75 80	79 46	0	1,198 74	23 4	51 1	+31 79			82
0 78	—	17 33	45 10	75 80	79 46	0	1,198 74	23 3	51 4	+27 77	0 108		80
0 64	—	17 28	45 10	75 80	79 46	0	1,198 74	23 3	51 3	+27 75			70
0 45	—	8 13	45 10	75 80	79 46	0	1,198 74	23 5	51 0	+36 96			74
1 38	—	15 87	45 10	75 80	79 46	0	1,198 74	23 6	50 7	+20 23	0 101		68
1 96	—	27 99	45 10	75 80	79 46	0	1,198 74	23 7	50 4	+17 11	0 136		80
1 83	—	20 13	45 10	75 80	79 46	0	1,198 74	23 7		+24 97			72
0 97	—	19 88	45 10	75 80	79 46	0	1,198 74	23 3	51 4	+25 22			76
1 31	—	23 72	45 10	75 80	79 46	0	1,198 74	23 2	51 5	+21 38	0 130		70
1 29	—	27 43	45 10	75 80	79 46	0	1,198 74	23 2		+17 67			78
1 95	—	27 85	45 10	75 80	79 46	0	1,198 74	23 6	50 7	+17 25			78
1 60	—	23 12	45 10	75 80	79 46	0	1,198 74	23 7	50 4	+21 98			70
1 65	—	25 13	45 10	75 80	79 46	0	1,198 74	23 7	50 4	+19 97	0 130		78
									50 4		0 114		80

—and Fluid Output

12–2 p m		2–4 p m		4–6 p m		6–8 p m		8–6 a m		Total	
Urine, C c	Sugar, Gm	Urine, C c	Sugar, Gm	Urine, C c	Sugar, Gm	Urine, C c	Sugar, Gm	Urine, C c	Sugar, Gm	Urine, C c	Sugar, Gm
83	2 59	99	2 40	118	2 77	305	7 50	340	6 83	1,643	27 99
251	8 21	347	3 36	266	4 15	210	2 12	396	6 75	2,040	23 72
584	3 27	370	2 96	372	5 39	145	2 75	320	7 20	2,546	27 43
204	4 38	134	3 12	140	3 15	176	1 83	315	6 48	1,458	27 85
172	3 44	112	2 29	117	2 31	200	1 50	285	5 13	1,440	23 12
200	5 00	170	3 06	154	3 54	238	1 83	270	6 61	1,612	29 13
			Diastolic	activity,	33						
			Diastolic	activity,	39						

3/30/17, Ambard's constant 0 09

in the diet being allowed During this time the glycosuria varied a great deal from day to day, although the chlorid metabolism was very low

Chart 2 is a graphic record of the glycosuria in relation to sodium bicarbonate ingested It will be noted this was during the same period as Section 2 of Chart 1, in other words, the chlorids were still restricted For a period of four days (A) before administration the daily average excretion was 10 9 gm Sodium bicarbonate in the amount indicated was then given by mouth This was continued for seven days and the average daily sugar excretion increased to 19 6 gm

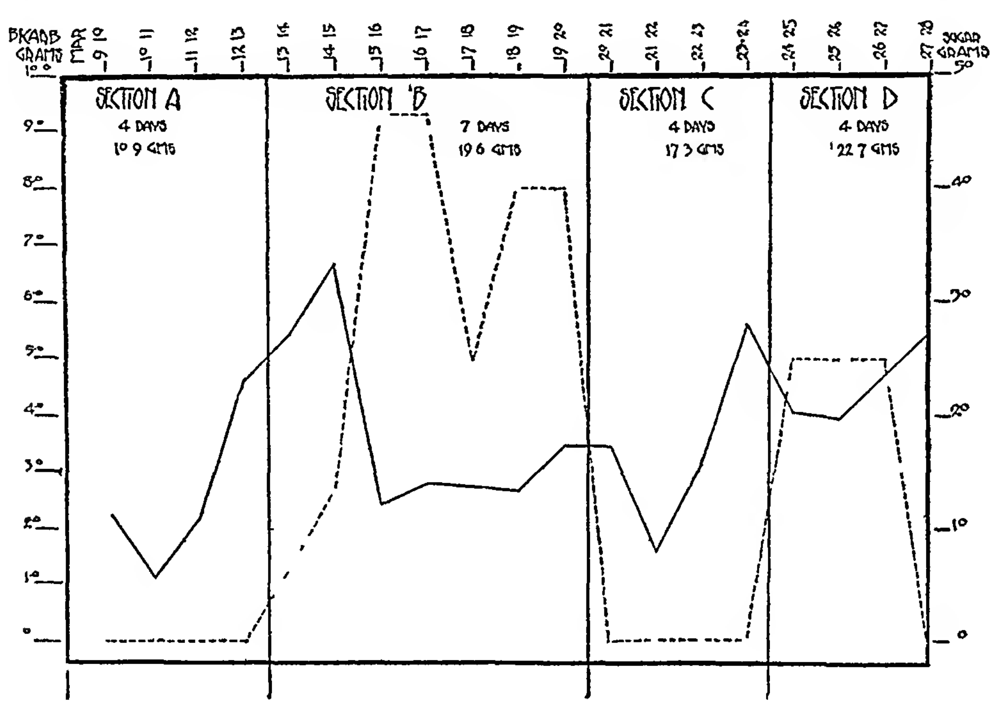

Chart 2—Graphic record of glycosuria in relation to sodium bicarbonate intake and sugar output Explained more fully in the text The dash line = sodium bicarbonate, solid line = sugar

A period of four days (C) without sodium bicarbonate was then given The average daily sugar output for this period was 17 3 gm The sodium bicarbonate was next given by duodenal tube for a period of three days (D), 1,000 c c of a 0 5 per cent solution being administered [21] During this period the daily sugar output averaged 22 7 gm It was felt that the bicarbonate was of little practical value, and we discontinued its administration During the remainder of the patient's stay in the hospital the daily sugar excretion averaged 25 gm of dextrose

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21 The duodenal contents were recovered at various periods in order to make certain the tube was in the duodenum Bile pigments were identified in the contents by the spectroscope

Table 2 records the sugar and fluid output During the day the urine was collected every two hours and a ten-hour collection made of the night specimen The patient was on the same diet each day and the salt was restricted throughout the entire period The first day is a record of the excretion with only the restricted salt Sodium bicarbonate was then administered by duodenal tube for four days Two hourly collections were made on the third and fourth days and are recorded on the table It will be noted that there is no appreciable change in the total output A return to three more days of restricted salt was then made

This table is of interest because of the amount of sugar excreted with each collection In the morning specimens the total output was always low, being about 1 to 2 gm During the middle of the day it increased at the same time the fluid output was at its height In the evening specimen it again fell to the same level as in the morning collection The night specimens were always low in total output Apparently no causal relationship exists between the fluid output and the glycosuria

It will be noted in Table 1 that the blood sugar[22] has been recorded at frequent intervals during the patient's entire stay in the hospital Only after prolonged starvation was there any appreciable change in the sugar level At that time it fell to 0 09 and 0 1 per cent During the period of constant diet in Table 2 it was between 0 12 and 0 14 per cent,[23] which is unquestionably the upper limit of normal

CONCLUSIONS

1 A diagnosis of renal glycosuria is established in this case

2 Glycosuria has little relation to chlorid metabolism in this condition

3 The renal threshold for sugar was not increased by sodium bicarbonate ingestion

The chlorids of the food were estimated from Sherman's "Chemistry of Food and Nutrition" In a few instances they were determined in our laboratory

Myers and Killian[24] have recently reported studies relative to the diastatic activity of the blood It is of passing interest that we record two determinations on this case The findings were 33 and 36, a little above the normal The prognostic significance of this is not yet apparent

24 Myers and Killian Jour Biol Chem, 1917, **29,** 179

We are indebted to Dr E L Tuohy of Duluth, who referred this case to the University Hospital, and to Miss Winifred Swift for technical assistance

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22 Blood collected some months after the patient left the hospital showed for oxalated blood, 0 0661 sugar, and for plasma, 0 060 sugar

23 We have found the normal limit in our laboratory between 0 11 and 0 14 per cent

SALT METABOLISM IN DIABETES MELLITUS * †

A H BEARD, M D
MINNEAPOLIS

During the last year, in addition to the routine followed in the metabolic wards of the University Hospital in the care and treatment of patients with diabetes mellitus, we have attempted to determine the cause and conditions leading to the rapid loss or gain of weight in patients suffering from this disease Any one working with diabetes has been surprised to note the gain in weight of certain types of patients while undergoing starvation It is not a new condition, arising entirely from[1] Allen's treatment In earlier days it was often found that patients gained weight on the "Oatmeal cures," or lost rapidly as coma approached

Rapid loss or gain in weight, the total calories remaining at the same level, occurs in normal individuals with alterations in amount of fat, carbohydrate and protein in their diets Joslin[2] asserts that a high carbohydrate diet is apt to increase the weight and a low carbohydrate with a high fat intake usually lowers it This is probably due to storage of one or the other of these ingredients Zuntz,[3] in 1912, showed that for every gram of carbohydrate stored in the body it was necessary to retain 3 gm of water, while, on the other hand, for every gram of fat retained, 0 1 gm of water was necessary As a result, it was thought that the rapid gain in weight on the old oatmeal diet was due to sudden storage of carbohydrates requiring the necessary amount of water in the body tissues

There are other factors that enter into the retention of fluids In normal individuals high sodium chlorid ingestion increases the weight of the body, although as a rule edema does not develop Joslin[2] mentions this in his recent monograph He also says that diabetic patients with the disease in severe form, during the starvation period, often develop edema, probably due to the high sodium chlorid ingestion In 1908 Joslin and Goodall[4] reported edema in severe diabetes following the use of sodium bicarbonate Their explanation was as follows

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† From the Chemical Laboratory, Department of Medicine, University of Minnesota

1 Allen Glycosuria and Diabetes, Boston, 1910
2 Joslin Treatment of Diabetes Mellitus, Lea & Febiger, 1916
3 Zuntz Biochem Ztschr, 1912, **44,** 290
4 Goodall and Joslin Jour Am Med Assn, 1908, **51,** 727

Apparently the administration of sodium bicarbonate by favoring the excretion of large quantities of retained acid bodies, leads to irritation of the kidneys, resulting in their inability to excrete salt in the normal manner If the salt in the diet is restricted there is less to be retained and consequently no gain in weight results

Joslin[2] also says that clinically it is inadvisable to allow a salt-free diet because of the liability of coma, in which loss of weight may be rapid

ROUTINE

On admission each patient was placed on a diet corresponding as closely as possible to the food intake before entrance to the hospital In a few instances, because of the condition of the patient, this has not been possible The cases showing moderate acidosis were included in the usual routine This gave us the actual condition of the patient before starvation was instituted The next step was preparation for starvation Fats were first restricted and later carbohydrates eliminated from the diet In other words, the acidosis received first consideration, the glycosuria being controlled later On the fourth day from 25 to 30 gm of carbohydrates were allowed, the amount of protein and fat being only that present in the 5 and 10 per cent vegetables and broth The fifth day started the complete starvation period, which was continued, in most cases, from two to three days, until glycosuria was eliminated Starvation consisted of the usual routine—broth, tea, and coffee without sugar or cream

Fluids were forced from the time of admission, the patient receiving between 2,000 and 3,000 c c of fluid daily [5] This also assisted in combating acidosis before starvation was instituted

The remaining routine was as follows

The patient was weighed daily before breakfast, after completion of the twenty-four-hour specimen The weight of the clothes was deducted in each case Later, after glycosuria had disappeared, the usual weekly starvation day was given

Alternate cases, irrespective of the severity of the disease, were placed in separate groups The first group was allowed unrestricted use of table salt without sodium bicarbonate The second group received sodium bicarbonate with only the chlorids normally present in the food Sodium bicarbonate was given in periods of from seven to ten days each, 10, 25 and 40 gm, respectively This grouping of patients excluded the possibility of selecting our cases for either type of treatment The food values were calculated by the hospital dietitian Sherman's[6] values were accepted for chlorid content of the food In

5 In each case the water content of the food was included

6 Sherman Chemistry of Food and Nutrition, Macmillan, 1915

a few instances the salt content was determined in our laboratory The broth was always made under the same directions and the chlorid determined twice a week in order to check the results As a rule, as presented to the patient, it averaged between 0 08 and 0 09 per cent[7] In the early cases the chlorid content of the feces was determined Because of the constant low excretion, between 0 2 and 0 8 gm in twenty-four hours, further determinations were discontinued The chlorid content of the blood was determined in the early cases by the McLean and Van Slyke[8] method Constant values between 5 5 and 6 2 mg per 100 c c, irrespective of edema, were found, and consequently these determinations were discontinued

The methods used in carrying out these studies were as follows

Determination	Method
1 Urinary nitrogen	Kjeldahl
2 Urinary ammonia	Rouchese Malfatti[9]
3 Urinary sugar	Benedict's solution and polariscope
4 Urinary diacetic acid	Gerhard's solution
5 Urinary acetone	Lugol's solution
6 Alveolar carbon dioxid	Collected—Plesch[10]
7 Alkaline reserve	Determined—Haldane[11]
8 pH of blood	Determined—Marriott[12]
9 Blood sugar	Van Slyke[13]
10 Chlorids of urine	Levy, Rowntree, and Marriott[14]
	Myers and Fine[15]
	Volhard-Harvey[16]

In the series of twenty-five patients varying between 5 and 78 years in age, edema and gain in weight developed in three patients Two developed edema on unrestricted chlorids (Cases 3 and 4), the third (Case 5) was given sodium bicarbonate with restricted salt The remaining patients showed a general loss of weight without edema, irrespective of the series in which they were placed Two of such typical cases are included in the report (Cases 1 and 2)

REPORT OF CASES

CASE 1—Mrs S (10834), aged 63, married, born in Sweden, lived in the United States thirty-five years, occupation, housewife, weight, 49 7 kg, height, 152 4 cm, admitted March 14, 1917, discharged May 12, 1917

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7 This was served to the patient In many instances they added large quantities of salt

8 McLean, F C, and Van Slyke, D D Jour Biol Chem, 1915, **21,** 361

9 Folin Laboratory Manual of Biological Chemistry, Appleton & Co, 1916

10 Plesch Ztschr f exper Path u Therap, 1909, **6,** 380

11 Haldane and Priestley Jour Physiol, 1905, **32,** 225

12 Marriott Jour Am Med Assn, 1916, **66,** 1594

13 Van Slyke Proc Soc Exper Biol and Med, 1915, **12,** 165

14 Levy, Rowntree, and Marriott THE ARCHIVES INT MED, 1915, **16,** 389

15 Myers and Fine Chemical Composition of the Blood in Health and Disease, 1915

16 Harvey THE ARCHIVES INT MED, 1910, **6,** 12

Family and past history negative

Present Illness—Four years prior to admission the patient developed weakness, polyuria, polydipsia and polyphagia and lost 90 pounds during this period A prescribed diet has not resulted in improvement Her physician says "she has never been sugar-free" Generalized pruritis has appeared during the last few months

Physical Examination—Considerable emaciation Heart and lungs are negative Abdomen is negative except for a palpable right kidney An old varicose ulcer is present over the left ankle and marked varicose veins are found in both legs Knee jerks not obtained

SUMMARY

This patient showed a gradual loss of weight On admission she was placed on restricted salt and the routine amounts of sodium bicarbonate for a period of four weeks It will be noted (Table 1) that her carbohydrate tolerance was first reached at 125 gm After the bicarbonate was discontinued, unrestricted chlorids were allowed A few days of digestive disturbance followed the withdrawal of the bicarbonate Later the carbohydrate tolerance was again reached at 125 gm This is of interest because of Underhill's[17] recent report claiming increased tolerance on sodium bicarbonate administration The metabolic and acid-base equilibrium studies are recorded in Table 1 Glycosuria and weight in relation to the salt and fluid balance have been recorded in Chart 1 Also the number of calories per kilogram body weight has been charted The highest chlorid intake in twenty-four hours was 21 gm The greatest loss of weight occurred in the first period during restriction of the chlorids On high sodium bicarbonate and unrestricted salt the weight was maintained It is only fair to state, however, that during the period of maintenance of weight the caloric intake was greater than during the earlier periods No edema developed at any time It will be noted that during her stay in the hospital there was a gradual loss of 12 5 pounds No marked chlorid and fluid retention or loss developed

Case 2—Mrs T (10530), aged 50, born in Belgium, lived in the United States fifteen years, occupation, housewife, weight, 65 8 kg, height, 1,473 cm, admitted Jan 27, 1917, discharged Feb 19, 1917

Family and past history are not remarkable

Present Illness began five or six years prior to admission with stiffness in knees, weakness and general malaise The skin was very "itchy" and the bowels have always been constipated The patient has been admitted in other hospitals but carbohydrate tolerance has never been determined There has been considerable polyphagia, polydipsia and polyuria The latter has decreased somewhat during the last few years There has been a gradual loss of 100 pounds in weight

Physical Examination—A poorly nourished, elderly woman, the heart is slightly hypertrophied and shows definite mitral insufficiency, umbilical hernia the size of an orange is present, both kidneys are palpable, knee jerks are not obtained

17 Underhill Jour Am Med Assn, 1917 **68,** 497

TABLE 1—Data—

Date 1917	Fluid Intake in C c.	Amt Urine in C c, 12 Hr	Specific Gravity	Reaction	Albumin	NH_3 Gm	Van Slyke	P H	CO_2 Tension in Mm Hg	Sod Bic, Gm	Sugar Excret % Reduct
March											
13-14		1,650	1 025	Acid	Tr	0 44			36 55	0	4 07
14 15	500(?)	1,075	1 015	Alk	Tr	?	41 48	7 40	38 79	0	1 46
15 16	2,680	2,500	1 010	Acid	Tr	0 575			38 09	4 0	0 38
16 17	2,769	2,450	1 008	Alk	S T	?			35 06	10 5	0
17 18	2,360	2,635	1 008	Alk	0	?			35 81	7 5	0
18-19	2,890	2,600	1 007	Alk	Tr	?				10 5	0
19 20	2,860	2,450	1 005	Alk	0	?	*47 74	7 40	29 84*	7 8	0
20 21	2,785	2,390	1 009	Alk	0	?			29 84	9 3	0
21 22	2,560	2,800	1 008	Alk	0	?			36 55	9 3	0
22 23	2,705	2,000	1 010	Alk	0	?			41 03	9 3	0
23 24	2,260	2,300	1 009	Alk	0	?	31 52		31 33	9 3	0
24 25	2,738	2,400	1 010	Alk	0	?			34 32	9 3	0
25 26	2,403	2,250	1 009	Alk	0	?				9 3	0
26 27	2,738	2,000	1 009	Alk	0	?			36 55	9 3	0
27 28	2,543	1,900	1 008	Alk	0	?			37 30	9 3	0
28 29	2,150	1,720	1 015	Alk	0	?			33 58	9 3	0
29 30	2,508	1,800	1 011	Alk	0	?	(Hem) 44 36	7 45	36 55	9 3	0 18
30 31	2,718	2,150	1 009	Alk	0	?			38 09	9 3	0
31 1	2,333	2,000	1 008	Alk	0	?				9 3	0
April											
1 2	1,885	2,625	1 012	Alk	0	?				23 3	0
2 3	2,331	2,450	1 012	Alk	0	?			38 09	27 0	0
3 4	2,010	2,650	1 016	Alk	0	?			57 37(?)	27 0	0
4 5	2,000	2 800	1 015	Alk	0	?			42 52	23 3	0
5 6	2 085	2,720	1 016	Alk	0	?	46 43	7 50		20 0*	0
6 7	1,935	2,400	1 015	Alk	0	?				20 0*	0 10
7 8	2,090	2 000	1 010	Alk	0	?				23 3	0
8 9	2,735	2,400	1 013	Alk	0	?				27 0	0
9 10	2,020	1,870	1 020	Alk	0	?	43 33		44 76	35 0	0
10 11	2,135	2,150	1 015	Alk	0	?			37 30	25 0	0
11 12	2,210	2,000	1 019	Alk	0	?			42 52	40 0	0
12 13	2,260	1,700	1 020	Alk	0	?	49 05	7 65	45 76	40 0	0 38
13 14	2,385	1,900	1 020	Alk	0	?			55 20	25 0	0 225
14 15	2,310	2 050	1 019	Alk	0	?			50 00	40 0	0
15 16	3,110	2 400	1 010	Alk	0	?				0	0
16 17	2,035	2,380	1 016	Alk	0	?			37 30	0	0
17 18	1,835	1,600	1 015	Alk	0	?	41 26		43 27	0	0

—IN CASE 1

Total Sugar Exc., Gm	C H Intake, Gm	Protein Intake, Gm	Fat Intake, Gm	Caloric Intake	Calories per Kg Body Weight	Weight, Kg	C H Bal	Blood Sugar, %	Blood Pressure	Pulse
67 15			General Diet							91
15 69	63 69	39 79	40 04	774 27	15 5	49 7	48 00	0 160		86
9 50	36 27	22 69	30 95	514 39	10 3	49 7	26 77			88
0	26 00	8 29	10 07	227 79	4 5	49 7	26 00			84
0	26 00	8 29	10 07	227 79	0	48 7	0			88
0	0	0	0	0	4 5	49 8	26 00			88
0	5 05	14 87	13 92	205 02	4 2	48 4	5 05			90
0	10 23	23 72	30 03	406 11	8 39	48 4	10 23			74
0	10 23	23 72	30 03	406 11	8 50	47 6	10 23			84
0	19 35	45 04	50 54	713 66	15 0	47 5	19 65			86
0	39 56	61 70	73 34	1,065 16	22 5	47 2	39 56			84
0	46 36	71 17	78 60	1,177 56	25 1	46 9	46 36			74
0	66 90	71 82	72 84	1,210 48	25 8	46 9	66 90			86
0	90 27	80 48	76 91	1,375 19	28 7	47 9	90 27			82
0	15 62	13 65	21 24	308 24	6 6	46 7	15 62			86
0	104 91	17 91	78 66	1,439 50	30 5	47 0	104 91			84
3 24	125 47	12 29	79 26	1,544 80	32 7	47 1	122 23	0 076		82
0	46 60	24 18	32 43	579 55	12 2	47 4	46 6			82
0	14 19	23 96	18 89	322 53	6 9	46 7	14 19			92
0	58 93	65 57	61 53	1,051 77	22 6	46 5	58 93			76
0	99 14	75 86	78 81	1,409 29	30 8	46 5	99 14		140/100	82
0	99 14	75 86	78 81	1,409 29	30 1	46 7	99 14	0 310		74
0	124 77	81 25	79 27	1,537 53	33 1	46 3	124 77			84
0	124 77	81 25	79 27	1,537 53	33 1	46 3	124 77	0 344		72
2 40	124 77	81 25	79 27	1,537 53	33 0	46 5	122 37			66
0	34 76	21 80	33 16	524 68	11 2	46 6	34 76			74
0	59 77	75 17	79 83	1,258 23	27 0	46 5	59 77			76
0	98 75	77 24	79 24	1,419 12	30 4	46 7	98 75	0 348		70
0	98 75	77 74	79 24	1,419 12	30 4	46 6	98 75			84
0	124 63	77 95	77 79	1,510 43	32 7	46 1	124 63			78
0 38	135 18	78 25	78 34	1,558 78	33 9	45 9	126 60	0 334		66
5 35	145 18	78 35	80 18	1,615 74	35 0	46 1	139 83			80
0	15 09	7 19	10 74	185 78	3 94	47 1	15 09			74
0	15 09	78 19	10 74	185 78	4 01	46 3	15 09			80
0	98 95	77 74	79 24	1,419 92	31 1	45 6	98 95			80
0	124 63	77 95	77 79	1,510 43	32 6	46 3	124 63	0 240		68

TABLE 1—DATA IN—

Date 1917	Fluid Intake in C c	Amt Urine in C c, 12 Hr	Specific Gravity	Reaction	Albumin	NH_3 Gm	Van Slyke	P H	CO_2 Tension in Mm Hg	Sod Bic, Gm	Sugar Excret % Reduct
18-19	1,560	1,460	1 020	Alk	0	?			32 08	0	0 60
19 20	2,810	2,270	1 010	Alk	0	?			38 09	1 0	0 95
20-21	1,700	1,400	1 015	Alk	0	?	39 06		39 45	0	0
21 22	2,260	1,200	1 017	Alk	Urates ++	?			32 08	0	0
22 23	1,800	1,470	1 020	Alk	Urates ++	?				0	0
23 24	1,710	1,620	1 012	Acid	0	0 615			32 08	0	0
24 25	2,925	1,700	1 010	Acid	0	1 58			34 32	0	0 042
25 26	1,775	1,500	1 015	Alk	0	?			36 55	0	0
26 27	3,025	1,700	1 010	Alk	0	?				0	0
27-28	2,835	1,840	1 018	Alk	0	?	43 88	7 45	42 52	0	0
28-29	2,775	2,040	1 011	Alk	0	?			37 30	0	0
29 30	2,600	1,650	1 013	Alk	0	?				0	0
30-1	2,600	2,600	1 010	Alk	0	?			37 30	0	0
May											
1 2	4,300	1,900	1 016	Alk	0	?			42 03	0	0
2 3	2,700	1,600	1 016	Alk	0	?			37 30	0	0
3 4	1,450	1,420	1 014	Alk	0	?			42 03	0	0
4 5	2,150	1,700	1 011	Alk	0	?				0	0
5 6	2,800	1,480	1 018	Alk	0	?			35 03	0	0
6-7	2,600	1,400	1 015	Alk	0	?				0	0
7-8	2,560	3,000	1 010	Alk	0	?			33 57	0	0
8 9	2,700	2,900	1 012	Alk	0	?			35 06	0	0
9 10	2,600	3,870	1 007	Acid	0	0 928			35 81	0	0
10 11	2,400	1,700	1 015	Alk	0				39 54	0	0
11 12	1,700	3,100	1 011	Alk	0				33 57	0	0

* Two determinations made Acetone and diacetic acid absent throughout No alcohol was used Sediment absent from urine

SUMMARY

A mild case of diabetes of six years' duration in which the patient was given unrestricted chlorids No edema developed and a gradual loss of 8 pounds occurred The tolerance was reached on 135 gm of carbohydrate The highest chlorid intake in one day was 31 gm Table 2 presents data relating to metabolism and acidosis Chart 2 shows the glycosuria and weight in relation to the salt and fluid balance

CASE 3—L V F (10541) aged 38 born in the United States, occupation chauffeur, weight 53 3 kg, height, 165 1 cm, admitted Jan 30, 1917, discharged Feb 23, 1917

—CASE 1—(*Continued*)

Total Sugar Exc., Gm	C H Intake, Gm	Protein Intake, Gm	Fat Intake, Gm	Caloric Intake	Calories per Body Weight	Weight, Kg	C H Bal	Blood Sugar, %	Blood Pressure	Pulse
8 76	114 32	70 49	86 11	1,514 23	32 9	46 1	105 56			118
21 56	76 86	60 42	98 76	1,438 00	31 1		55 30			92
0	13 71	10 70	11 40	200 24	4 4	45 2	13 71	0 294		86
0	40 13	37 95	38 48	658 64	14 7	44 6	40 13			90
0	40 13	37 95	38 48	658 64	14 9	44 0	40 13			90
0	49 75	56 08	56 04	827 68	18 8	44 0	49 75			88
0 714	66 13	55 86	55 45	987 01	22 2	44 3	65 42			82
0	82 07	66 47	69 13	1,216 33	27 2	44 5	82 07			82
0	14 58	22 58	19 62	314 07	6 97	45 0	14 58			100
0	39 68	34 92	38 72	646 88	14 5	44 5	39 68	0 177		80
0	59 73	55 41	55 39	959 07	21 2	45 2	59 73			78
0	60 44	56 20	64 78	1,049 58	23 4	44 7	60 44			72
0	62 39	56 69	65 22	1,063 30	23 8	44 7	62 39			92
0	62 39	56 39	65 22	1,065 30	23 8	44 6	62 39			80
0	54 67	53 31	55 18	928 54	20 6	45 0	54 67			86
0	54 67	53 31	55 18	928 54	20 6	45 0	54 67	0 246		86
0	61 01	53 81	59 47	994 51	22 1	44 9	61 01			70
0	15 85	7 41	8 60	169 36	3 7	45 1	15 85			86
0	69 77	57 22	64 91	1,092 15	24 5	44 5	69 77			84
0	69 77	57 22	64 91	1,092 15	24 3	44 8	69 77			84
0	81 30	60 54	77 20	1,262 16	28 1	44 9	81 30			86
0	81 30	60 54	77 20	1,262 16	28 3	44 5	81 30			88
0	100 34	67 34	70 67	1,311 01	29 8	44 0	100 40			90
0	122 08	78 39	76 99	1,494 79	33 4	44 7	122 08			82

Family and past history are negative

Present Illness—This began gradually, one year prior to admission, with progressive loss of weight, pain in the legs and polyuria Later polyphagia and polydipsia appeared One month previous to admission a diagnosis of glycosuria and diabetes was made The patient's diet has been moderately restricted since that time There have been no symptoms suggesting threatened coma His highest weight three years before admission was 150 pounds One year before admission he weighed 125 pounds

Physical Examination—A well developed and fairly nourished young man There is slight cyanosis of the lips and some internal strabismus, which he says "has been present since childhood" Otherwise the physical findings are negative

Phenolsulphonephthalein excretion, Feb 2 1917 first hour, 34 per cent second hour, 15 per cent , total 49 per cent

SUMMARY

This case has been recorded because of the severity of the acidosis and glycosuria The patient left the hospital before his tolerance was established The dextrose-nitrogen ratio is of little value, since he received some carbohydrates in the form of milk on the fifth and sixth days Table 3 records his metabolism and acidosis studies It will be noted (Table 3) that he was allowed unrestricted chlorid and took as high as 47 gm in twenty-four hours He gained 9 5 pounds during his first week after admission During this period the chlorid intake

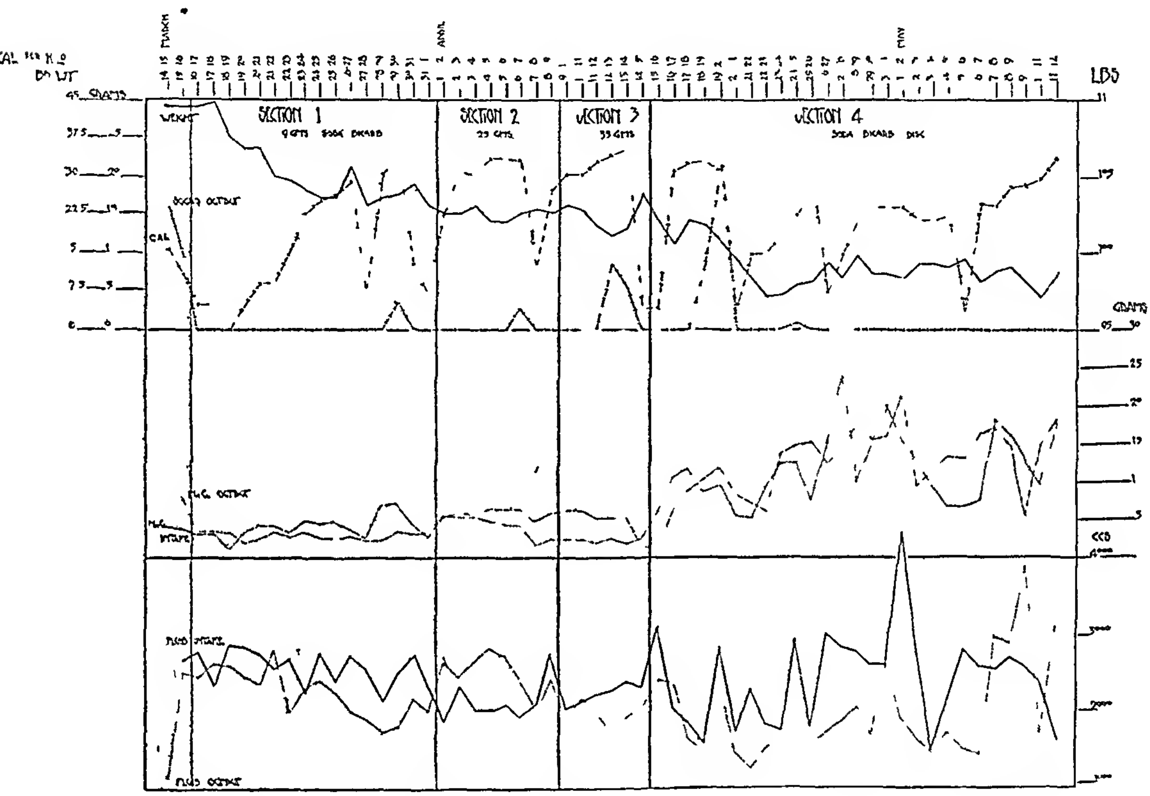

Chart 1—Curves showing glycosuria and weight in relation to the salt and fluid balance in Case 1

was 136 14 gm, and his elimination 122 16, showing a retention of 13 98 gm At the same time his fluid intake was 22,483 c c, and his output 20,550 c c, with a urinary retention of 1,933 c c The next seven days showed an increased dextrose elimination while on a protein and fat diet At the same time his chlorid intake fell and his chlorid excretion was greater than his ingestion During this period he excreted 211 82 gm and the intake was 60 55 gm, or a difference of 151 27 gm His fluid balance showed an intake of 28,045 c c and an output of 26,400, with a urinary retention of 1,645 c c (probably excreted through skin and lungs) He lost 7 5 pounds during this period The glycosuria shows a definite increase and the sugar curve

corresponds to the chlorid elimination Otherwise the chart (Chart 3) does not show anything of interest Edema was present after the second day of admission being most marked during the first week

Case 4—S E (10431), aged 18 years, single, born in the United States, occupation, farmer, weight 49 2 kg , height 160 cm His first admission to this hospital was in 1915 He became sugar-free on a moderately restricted diet The carbohydrate tolerance was not determined

Present admission, Jan 17, 1917, discharged Feb 16, 1917

Family and past history negative

Present Illness—Two years ago (April, 1915) the patient developed painful urination and considerable frequency Some polyuria appeared The com-

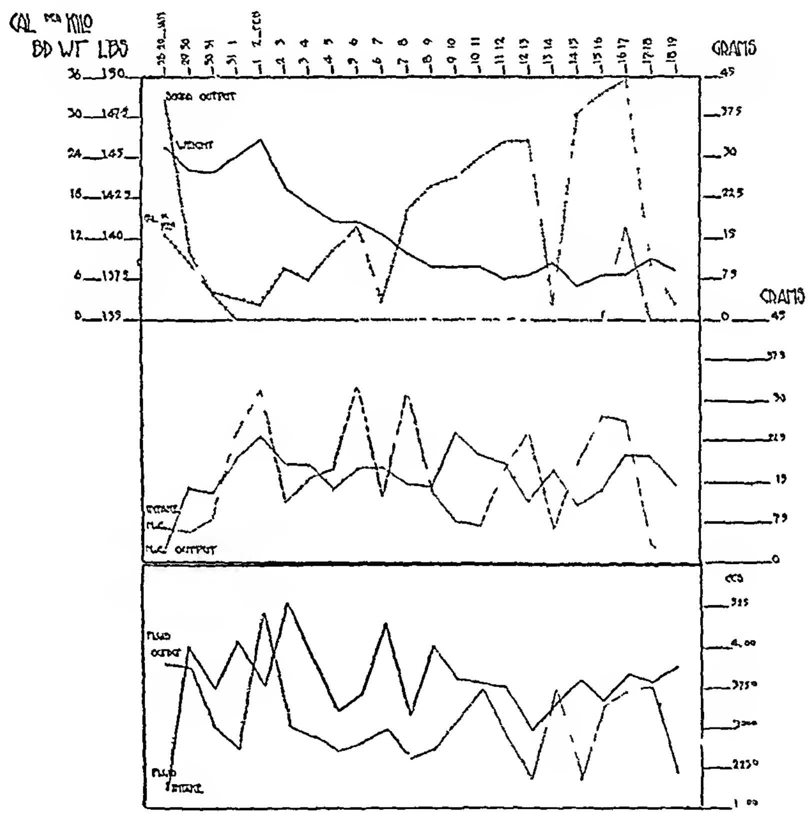

Chart 2—Curves showing glycosuria and weight in relation to salt and fluid balance in Case 2

bination was so severe that he suffered considerably from insomnia Later polydipsia and polyphagia developed Four months later a carbuncle was opened on the back of his neck and on reporting to his physician, diabetes was discovered At this time severe headache with some nausea and vomiting occurred These symptoms had disappeared at the time of his first discharge from the hospital During the last few weeks symptoms of acidosis with threatened coma have again developed His father said "He has had considerable headache, nausea, and vomiting, diarrhea and drowsiness during the last two weeks He has lost 20 pounds in the last two years, none recently"

Physical Examination—A well developed and fairly well nourished young man, very drowsy and aroused with difficulty, mucous membrane slightly cyanotic, otherwise physical examination is negative

Phenolsulphonephthalein excretion, Jan 17, 1917 first hour (500 c c), 70 per cent , second hour, 30 per cent

TABLE 2—DATA—

Date 1917	Fluid Intake in C c	Amt Urine in C c, 12 Hr	Specific Gravity	Reaction*	NH3 Gm	Van Slyke	P H	CO2 Tension in Mm Hg H	CO2 Tension in Mm Hg M	Sod Bic, Gm	Sugar Excret % Reduct
Jan											
27 28		420	1 025	Alk	?	37 32	7 3	39 54	40	0	1 47
28 29	1,850	4,225	1 010	Acid	1 23					0	0 958
29 30	4,518	4,125	1 006	Acid	1 32			42 52	40	0	0 301
30-31	3,750	3,000	1 009	Acid	1 16			37 30	40	0	0 150
31 1	4,600	2,600	1 009	Acid	?	27 25	7 3	36 55		0	0
Feb											
1 2	3,800	5,125	1 005	Alk	?			34 32		0	0
2 3	5,300	3,000	1 009	Alk	1 24			32 82	35	0	0
3 4		2,800	1 010	Acid	?			32 82	35	0	0
4 5	3,350	2,550	1 009	Alk	0 56					0	0
5-6	3,622	2,700	1 010	Acid	?			38 79	40	0	0
6 7	4,900	2,950	1 010	Alk	?			34 32	35	0	0
7 8	3,190	2,400	1 009	Alk	?			35 81		0	0
8-9	4,448	2,600	1 009	Alk	?	41 51	7 4	42 52		0	0
9 10	3,928	3,100	1,008	Alk	?			41 03		0	0
10-11		3,700	1 010	Alk	?			39 54		0	0
11-12	3,699	2,800	1 010	Alk	?					0	0
12 13	2,904	2,050	1 011	Alk	?					0	0
13-14	3,424	3,700	1 006	Alk	?			43 27		0	0
14 15	3,910	2,000	1 009	Alk	?			41 78		0	0
15-16	3,525	3,400	1,007	Alk	?			44 01		0	0
16 17	4,010	3,700	1 011	Acid	0 88			43 27		0	0 460
17 18	3,873	3,750	1 006	Neg	1 72	43 67		41 03		0	0
18 19	4,185	2,150	1 011	Acid	0 64					0	0
19 20	3,500					44 52				0	0

* January 27 28, acetone +, diacetic acid doubtful, otherwise negative throughout, albumin, a trace January 28-29, sediment absent, no alcohol given

SUMMARY

This patient showed symptoms of threatened coma on admission The glycosuria decreased from 102 gm to zero in four days Associated with this there was a decrease of the acidosis The carbohydrate tolerance was from 35 to 40 gm He was allowed unrestricted chlorid and it will be noted that in the first period he ingested as high as 37 gm in twenty-four hours

The metabolic and acidosis studies are recorded in Table 4 The acidosis studies showed a steady tendency to return to normal and on

—IN CASE 2

Total Sugar Exc , Gm	C H Intake, Gm	Protein Intake, Gm	Fat Intake, Gm	Caloric Intake	Calories per Kg Body Weight	Weight, Kg	C H Bal	Blood Sugar, %	Blood Pressure	Pulse
6 17				General Body						84
40 55	99 97	28 16	28 36	767 76	12 54	66 0	59 42			76
12 41	64 61	21 38	20 81	526 75	8 5	65 4	52 21			83
4 5	39 32	8 76	8 11	265 31	4 06	65 3	34 32		120/80	78
0	15 26	8 76	6 29	152 33	?		15 26	0 485		88
0	15 26	8 67	6 29	152 33	2 3	66 3	15 26			90
0	25 68	26 59	30 02	479 26	7 3	64 9	25 68			79
0	19 74	19 58	23 95	370 83	5 7	64 4	19 74			88
0	30 82	39 57	40 44	645 66	10 0	64 0	30 82			92
0	39 20	53 11	55 11	865 23	13 5	64 0	39 20			85
0	15 26	8 67	6 29	152 33	2 4	63 6	15 26			84
0	51 73	60 36	65 84	1,050 92	16 6	63 1	51 73			88
0	60 23	61 16	82 94	1,232 02	19 4	62 7	60 23	0 279		89
0	69 51	66 54	87 41	1,330 89	21 2	62 7	69 51			92
0	81 00	72 17	99 03	1,503 95	23 9	62 7	81 00			92
0	90 51	71 39	110 21	1,639 49	26 2	62 4	90 51			91
0	95 99	69 93	108 12	1,646 66	26 3	62 5	95 99			89
0	14 79	7 90	6 14	146 02	2 4	62 8	14 79			90
0	117 79	70 72	125 24	1,881 20	30 2	62 2	117 79			84
0	135 55	74 82	140 47	2,105 71	33 7	62 5	135 55			92
17 02	157 82	65 36	147 52	2,220 40	35 7	62 5	140 80			82
0	34 16	18 41	35 04	525 64	8 3	62 9	34 16			80
0	14 19	7 90	6 14	146 02	2 3	62 6	14 19	0 288		76
0						62 7				78

discharge a normal acid-base equilibrium was present Chart 4 records the usual curves of glycosuria and weight in relation to chlorid and fluid balances During Period 1 the chlorid intake was 143 gm and his output 84 gm, showing a retention of 58 3 gm of sodium chlorid The fluid chart records an intake of 26,009 c c and an output of 15,270 c c There was a retention of 10,739 c c, or a daily retention of 1,789 c c During this period there was an increase of 13 pounds in weight with considerable edema of the ankles

During the ten days after glycosuria disappeared the weight gradually decreased to the level present on admission He excreted

214 gm of sodium chlorid while the chlorid intake was only 72 8 gm —a loss of 141 2 gm The fluid ingested was 34,155 c c, and the excretion 27,750 c c —a retention of 6,405 c c There was a daily retention of 640 c c Glycosuria did not occur with the chlorid excretion as in Case 3 The second period of sugar excretion occurred at the time his tolerance was reached Following this period he again ingested a large amount of chlorids, which he retained (Section 3, Chart 4) Later a slight gain in weight occurred At this time a third

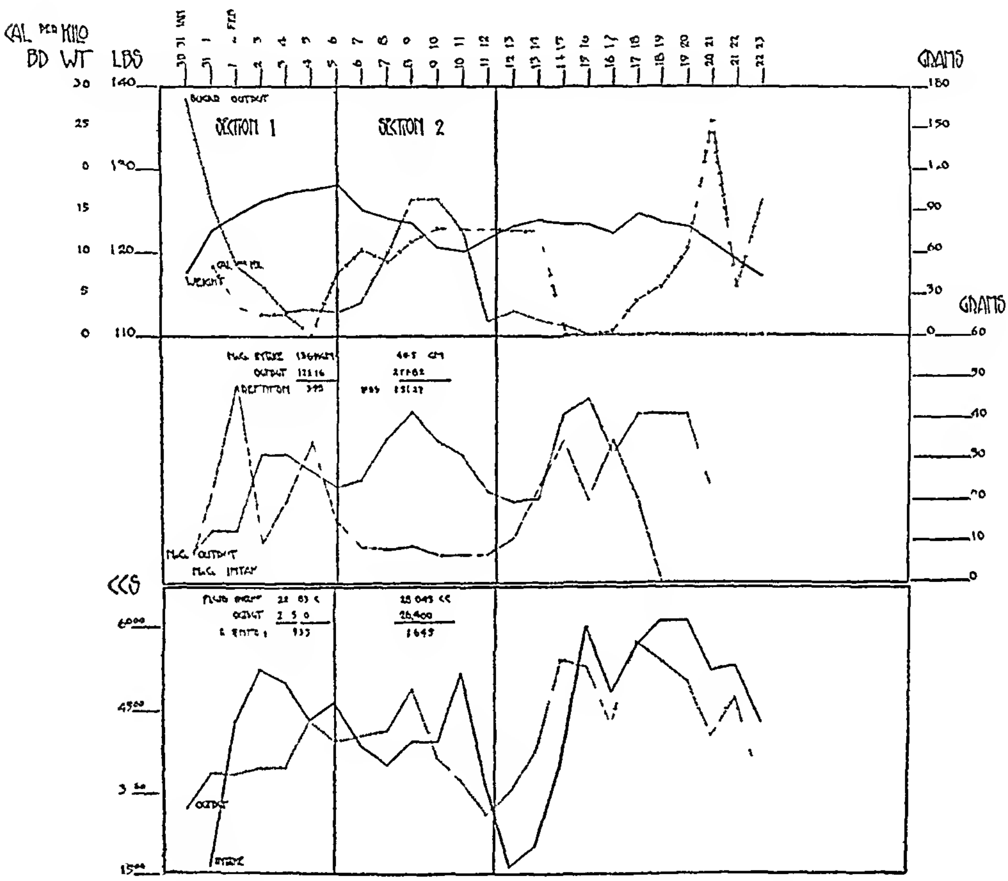

Chart 3—Curves showing findings in Case 3, a definite increase in the sugar curve corresponding to the chlorid elimination

period of glycosuria developed and simultaneously the retained chlorids were excreted

During the second period the carbohydrate tolerance occurred on 49 38 gm At this time there was edema and a gradual loss of weight After he had returned to his admission weight and the edema had disappeared, the tolerance was 37 48 gm of carbohydrate This is the only case showing an increased carbohydrate tolerance in the group of unrestricted chlorids

CASE 5—Mrs L H (10927), aged 26, born in the United States, occupation, housewife, weight 37 9 kg, height 136 cm, admitted March 27, 1917, discharged April 29, 1917 Maternal grandfather had diabetes, died at age of 87 Otherwise the family and past history are negative

Present Illness—One year prior to admission the patient developed weakness and gradually lost 60 pounds in weight At that time she was pregnant The child now is 10 months old and doing nicely There has been excessive polyuria, polydipsia, and polyphagia, has been on a modified Allen treatment for nine months, but glycosuria has persisted Tolerance has never been determined Amenorrhea has existed for seven months, with considerable pain in back and legs

Physical Examination —A poorly developed and undernourished young woman, slight general adenopathy, lungs show some impairment of right apex slightly more than physiologic, no râles made out on repeated examination, but expiration is prolonged, liver dulness begins at the fourth rib and is lost 1 cm below the costal margin, where a smooth edge is felt Both kidneys are palpable

Phenolsulphonephthalein excretion first hour, 34 per cent, second hour, 12 per cent, total, 46 per cent

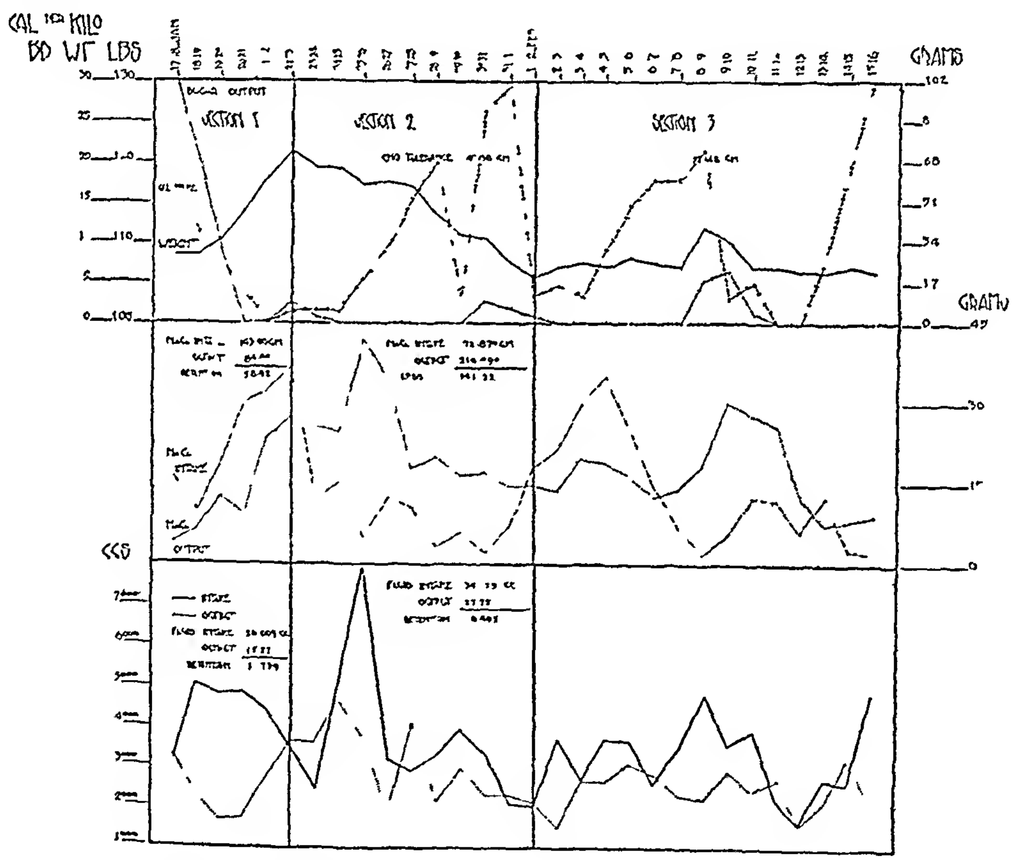

Chart 4—Curves showing glycosuria and weight in relation to chlorid and fluid balances in Case 4 *Food stolen

SUMMARY

Mrs L H was the only patient showing increase of weight on sodium bicarbonate ingestion Table 5 records the metabolic and acidosis studies Chart 5 records the glycosuria and weight in relation to chlorid and fluid balances It will be noted that during the period of sodium bicarbonate administration the chlorids were restricted During this period there was a gain of 10 pounds in weight At vari-

TABLE 3—Data—

Date 1917	Fluid Intake in C c	Amt Urine in C c, 12 Hr	Sp Gr	Reaction	Acid* A	Acid* D	D N Ratio	NH_3 Gm	Van Slyke	P H	CO_2 Tension in Mm Hg H	CO_2 Tension in Mm Hg M	Sod Bic
Jan													
29 30		3,100	1 028	Acid	1,226 Mgm ++	++		2 17			37 30	35	0
30 31	2,000	2,700	1 034	Acid	1,263 6 Mgm ++	++		3 07	29 53	7 35	32 08	30	0
31 1	1,568	3,350	1 019	Acid	1,632 0 Mgm +	+		3 88			29 85	30	0
Feb													
1 2	4,300	3,350	1 018	Alk	+	0		?			30 59	30	0
2 3	5,250	3,400	1 016	Acid	Tr	+		3 10			34 32	35	0
3 4	5,065	3 450	1 013	Acid	+	+		2 69			34 32	35	0
4 5	4,300	4,300	1 013	Acid	Tr	+		2 45					0
5-6	4,615	3,900	1 012	Acid	Tr	+	0 953	2 34	34 48	7 40	38 09	40	0
6 7	3,800	4,000	1 013	Acid	++	+	1 10	2 32	35 72	7 40	38 79	40	0
7 8	3,580	4,100	1 020	Acid	++	+	2 70	2 33	36 58	7 40	33 79		0
8 9	3,900	5,000	1 020	Acid	++	+	3 26	3 20	32 77	7 40	35 81		0
9 10	3,900	3,600	1 024	Acid	++	++		3 34	29 53	7 35	35 81		0
10-11	5,150	3,200	1 016	Acid	++	+		2 41	32 77	7 35	38 79		0
11 12	3,100	2,600	1 016	Acid	++	+	1 14	1 07					0
12-13	1,600	3,000	1 012	Acid	Tr	0	2 10	1 62					0
13 14	2,050	3,700	1 009	Acid	+	Tr	1 00	1 51	40 43		38 79		0
14 15	3,400	5,400	1 008	Acid	+	0	0 366	1 72			40 28		0
15-16	6,000	5,300	1 009	Alk	0	0		?	40 64	7 40	42 52		0
16 17	4,800	4,200	1 008	Acid	Tr	Tr		1 02	42 57		45 51		0
17-18	5,700	5,750	1 012	Acid	0	0		1 38			42 52		0
18 19	6,100	5,400	1 012	Acid	0	0		1 83			?		0
19 20	6,100	5,000	1 006	Acid	+	+		1 20			38 09		0
20 21	5,200	4,000	1 010	Acid	0	0		1 49					0
21 22	5,350	4,700	1 009	Alk	0	0		?			41 03		0
22 23	4,250	3,100	1 009	Alk	0	0		?					0
23 24	4,710								42 36	7 40	42 52		0

* Albumin and sediment absent, no alcohol used

P S P 2 2-17 First hour 34%
Second hour 15%
Total 49%

—IN CASE 3

Sugar Excret % Reduct S	B	Total Sugar Exc, Gm	C H Intake, Gm	Protein Intake, Gm	Fat Intake, Gm	Caloric Intake	Calories per Kg Body Weight	Weight, Kg	C H Bal	Blood Sugar, %	Blood Pressure	Pulse
6 8	7 2	223 51			General Diet						104/80	80
6 2	6 32	170 64			General Diet			53 3		0 630		70
2 8	2 81	94 13	50 93	19 17	20 14	461 66	8 3	55 6	—43 2			80
1 5	1 57	52 60	25 88	9 42	6 46	199 34	3 52	56 5	—20 72			64
	1 06	36 04	15 26	8 67	6 29	152 33	2 66	57 2	—20 78			62
0 50	0 51	17 59	15 26	8 67	6 29	152 33	2 64	57 6	—2 33			66
0 30	0 42	18 06	0	0	0	0	0	57 9	—18 06			60
0 40	0 45	17 55	0	31 90	32 82	422 98	7 28	58 1	—17 55	0 243		68
0 40	0 58	23 20	0	47 70	43 97	586 53	10 3	56 7	—23 20			62
0 70	1 49	59 74	0	38 85	38 99	506 31	8 99	56 3	—59 74	0 321		56
1 7	1 93	96 5	0	45 50	49 24	625 16	11 15	56 0	—96 5	0 332		76
2 2	2 69	96 84	0 (?)	52 10	55 24	705 56	12 9	54 7	—96 8	0 435		88
	2 30	73 6	0 (?)	52 10	55 24	705 56	12 9	54 5	—73 60	0 352	100/78	88
	0 40	10 4	0	52 10	55 24	705 56	12 8	55 1	—10 4			80
0 50	0 59	17 7	0	52 47	55 24	708 66	12 7	55 8	—17 7			92
0 20	0 30	11 1	0	52 47	55 24	708 66	12 6	56 1	—11 1	0 304		88
0 10	0 12	6 48	0	0	0	0	0	56 0	—6 48			92
0		0	0	0	0	0	0	56 0	0	0 276		74
0		0	0	2 20	2 00	26 8	0 48	55 4	0	0 276		78
0		0	5 18	15 39	16 82	233 66	4 1	56 5	+5 18			66
0		0	11 90	17 40	23 64	329 96	5 89	56 0	+4 13			70
0		0	14 96	36 67	41 39	579 03	10 3	55 8	+14 96			72
—0 1	0	0	20 36	43 43	44 88	1,400 34	25 5	54 9	+20 86	0 258		68
—0 1	0	0	11 88	10 54	25 58	319 90	5 92	54 0	+11 88			80
—0 1	0	0	15 94	34 64	74 14	869 58	16 3	53 1	+15 94			82
										0 292		70

TABLE 4—Data—

Date 1917	Fluid Intake in C c	Amt. Urine in C c, 12 Hr	Sp Gr	Reaction	Acid		Albumin	Sediment	NH_3 Gm	Van Slyke	P H	CO_2 Tension in Mm Hg		Sod Bic
					A	D						H	M	
Jan														
16-17		1,750	1 012	Acid	++	+	0	Gran casts	1 52	30 5		30 59	30	0
17 18	3,200	3,250	1 016	Acid	++	+	0	Gran casts	2 83					0
18-19	5,125	2,300	1 018	Acid	++	++	0	Gran casts	3 10			30 00		0
19 20	4,829	1,675	1 016	Acid	++	+	0	0	1 78					0
20 21	4,850	1,725	1 014	Alk	+	+	Tr	0	?				35	0
21 22	4,480	2,670	1 015	Alk	++	+	0	0	?					0
22 23	3,525	3,650	1 012	Alk	+	0	Tr	0	?	41 08	7 4		40	0
23 24	2,500	3,600	1 012	Acid	S T	0	0	0	1 68			38 79	39	0
24-25	5,150	4,700	1 009	Alk	0	0	0	0	?			39 54	38	0
25-26	7,875	3,800	1 013	Alk	0	0	0	0	?				35	0
26-27	3,225	1,875	1 011	Alk	0	0	0	0	?			31 33	30	0
27 28	2,875	4,075	1 009	Alk	0	0	0	0	?			37 3	35	0
28-29	3,325	2,150	1 008	Alk	0	0	0	0	?					0
29 30	3,855	2,950	1 008	Alk	0	0	0	0	?					0
30-31	3,300	2,300	1 012	Alk	0	0	0	0	?	41 50	7 4	38 57	35	0
31 1	2,050	2,300	1 009	Alk	0	0	0	0	?			34 5		0
Feb														
1-2	2,040	2,100	1 012	Acid	0	0	0	0	0 85			33 57	35	0
2 3	3,750	1,500	1 010	Acid	0	0	0	0	0 35					0
3 4	2,685	2,700	1 011	Alk	0	0	0	0	?			38 09	35	0
4-5	3,700	2,680	1 009	Acid	0	0	0	0	0 73					0
5-6	3,638	3,100	1 011	Acid	0	0	Tr	0	0 87	43 71	7 45	39 54	40	0
6-7	2,575	2,800	1 010	Alk	0	0	0	0	?			43 27	40	0
7 8	3,465	2,300	1 019	Alk	0	0	0	0	?			38 09	40	0
8-9	4,805	2,200	1 015	Acid	Tr	+	0	0	0 66	41 05	7 45	43 27		0
9 10	3,550	2,900	1 014	Acid	+	+	0	0	2 32			39 54		0
10-11	3,900	2,400	1 014	Acid	0	Tr (?)	0	0	0 82			43 27		0
11 12	2,200	2,700	1 010	Acid	0	0	0	0	0 30					0
12 13	1,600	1,600(?)	1 010	Alk	0	0	0	0	?					0
13 14	2,650	2,150	1 009	Alk	0	0	0	0	?			40 28		0
14 15	2,599	3,200	1 008	Alk	0	0	0	0	?			45 51		0
15-16	4,859	2,200	1 008	Acid	0	0	0	0	1 01	45 19	7 45	44 76		0

* No alcohol given
P S P 1-17 17 First hour [500 c c] 70%
Second hour 30%

—IN CASE 4

Sugar Excret % Reduct S	B	Total Sugar Exc, Gm	C H Intake, Gm	Protein Intake, Gm	Fat Intake, Gm	Caloric Intake	Calories per Kg Body Weight	Weight, Kg	C H Bal	Blood Sugar, %	Blood Pressure	Pulse
	3 11	54 35				General	Diet			0 380		74
3 0	3 14	102 05	101 94	41 83	21 09	762 89	15 5	49 2	—0 11			80
2 9	3 03	69 69	70 27	22 99	20 10	553 94	11 2	49 2	+0 58			68
2 0	1 84	30 82	39 82	15 76	18 53	384 09	7 74	50 0	+8 5			62
0		0	21 45	10 49	7 27	195 89	3 79	51 7	+21 45			62
0		0	0	0	0	0	0	53 6	0			74
0 24	0 23	8 57	0	6 60	6 00	80 4	1 46	55 0	—8 57	0 237		52
0 10	0 085	3 06	0	6 60	6 00	80 4	1 48	54 1	—3 06			62
0		0	0	6 60	6 00	80 4	1 48	54 1	0			72
0		0	15 26	17 13	17 93	190 93	5 46	53 2	+15 26			58
0		0	20 20	30 26	36 12	526 92	9 88	53 3	+20 20			62
0		0	30 70	52 51	55 01	827 93	15 6	53 1	+30 70			58
0		0	41 16	59 21	69 70	1,028 78	19 9	51 5	+41 16			64
0		0	15 26	8 67	6 29	152 33	3 02	50 4	+15 26			62
0 30	0 42	9 66	49 38	56 65	99 32	1,318 00	26 3	50 1	+39 72	0 222		90
	0 28	6 44	61 26	58 54	109 18	1,461 82	29 8	48 9	+54 82			94
	0 12	2 54	15 26	8 67	6 29	152 33	3 17	48 0	+12 72			94
0		0	15 26	15 27	12 29	232 73	4 8	48 6	+15 26			65
0		0	15 26	8 67	6 29	152 33	3 17	48 8	+15 26			82
0		0	19 74	26 17	29 95	453 19	9 3	48 6	+19 74			68
0		0	26 30	41 86	49 93	722 01	14 7	49 0	+26 30	(Plasma) 0 162		70
0		0	39 20	53 11	55 11	865 23	17 7	48 8	+39 20	0 305		92
0		0	39 20	53 11	55 11	865 23	17 7	48 6	+39 2			94
0 86	0 86	18 92	37 48	65 68	74 13	1,079 81	21 2	50 9	+18 56	0 316		104
	0 77	22 33	15 26	8 69	6 29	152 33	3 05	49 9	—7 06			72
	0 20	4 8	15 26	11 23	26 43	243 83	5 01	48 6	+10 46			80
0		0	0	0	0	0	0	48 6	0			84
0		0	0	0	0	0	0	48 3	0			84
0		0	13 59	22 63	27 43	391 43	8 1	48 3	+13 59			96
0		0	28 61	53 10	70 03	957 11	19 6	48 6	+28 61			70
0		0	35 37	60 70	120 79	1,471 39	30 5	48 3	+35 37	0 207		92

ous times glycosuria developed As shown in the first section of the chart the tolerance was reached on 53 gm of carbohydrate The second section shows glycosuria occurring on 70 gm of carbohydrate Section 3 is of little importance because of the short period On discontinuing the bicarbonate, unrestricted chlorids were allowed (Section 4) Glycosuria now occurred, first on 55, and later on 49 gm of carbohydrate This is the only case in the bicarbonate group showing an increased tolerance Here, as in the former case, the tolerance varied with an increase of weight and the development of edema At that time the reaction of the blood was normal and the glycosuria was

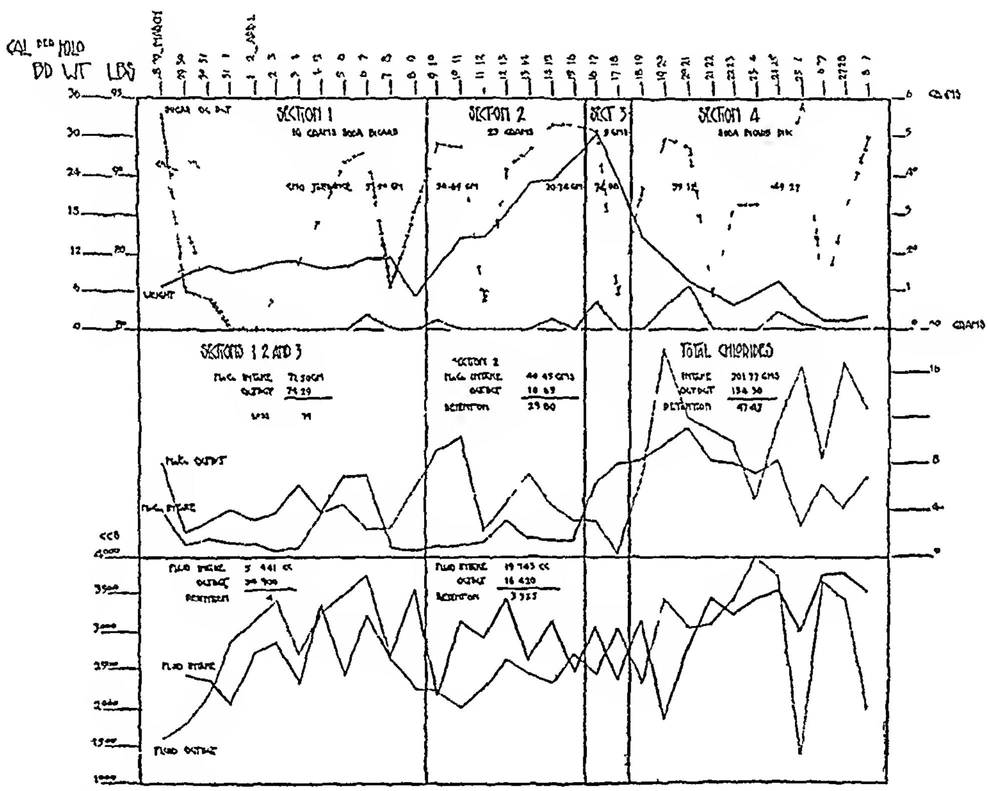

Chart 5—Curves showing the glycosuria and weight in relation to salt and fluid balance in Case 5

not considered to be the result of the withdrawal of sodium bicarbonate

As shown in Sections 1, 2 and 3, there was a total of 74 2 gm of chlorids excreted and 72 5 intake, giving a loss of 1 79 gm During this time the fluid intake and output balanced remarkably As shown in Section 2, during the greatest gain in weight, there were 40 45 gm of salt taken in the diet and 10 65 gm excreted, showing a retention of 29 80 gm At this time the fluid intake was 19,743 c c and the excretion, 16,420 c c —a low retention of 3,323 c c (475 c c per day) During the time shown in Section 4 the chlorids were unrestricted and

the highest daily intake was 18 gm The total chlorids ingested were 201 77 gm and the total excreted were 154 3 gm, giving a retention of 47 47 gm At this time 32,040 c c of fluid were ingested and 31,015 c c excreted with a retention of 1,025 c c It will be noted that, although the patient retained chlorids, she continued to lose weight, and edema gradually disappeared The loss in weight cannot be accounted for in the fluid balance The fluid retention is overbalanced by loss from lungs and skin

As shown in Section 1, she was able to maintain her weight, although a low caloric diet was given In the second period, a period of high caloric intake, she gained markedly in weight In Section 4 it is shown that with the coloric intake per kilogram of body weight slightly decreased, she lost weight rapidly

DISCUSSION

It is of interest to note the age of the patient developing edema Edema occurred in the young individuals If the edema had been due to kidney irritation we could have imagined the older individuals more readily showing an increase of weight Cases 1 and 2, patients without edema, were aged 63 and 50 years, respectively In the series of twenty-five cases only two patients showed kidney impairment by the usual studies available, and, although allowed unrestricted chlorids, they did not show any edema The three patients in whom edema appeared were between 18 and 36 years, and had had the disease from one to two years There were other patients showing no edema who had had the disease only a few months, with a constant loss in weight This is true in children, of which there were five, varying between 5 and 14 years

This report would have been of greater value if the patients could have been studied in the calorimeter, nevertheless, there are a few interesting results to be mentioned The relation between glycosuria and retention of fluids is not constant Only Case 4 showed any marked retention of fluid The apparent slight retention in the other cases could be accounted for by loss of fluid through the other routes available None of the patients developed diarrhea, but the skin and respiratory loss could not be recorded In Case 3 glycosuria developed during the period of edema and gain in weight In Cases 4 and 5 glycosuria did occur, but appeared only as the tolerance was reached The charts do not show any consistent retention of carbohydrate due to the retention of fluids During the period of loss of weight, it might have been expected that glycosuria would occur as the patient lost edema Glycosuria did occur, but in each case the tolerance had been reached

TABLE 5—DATA—

Date 1917	Fluid Intake in C c	Amt Urine in C c, 12 Hr	Sp Gr	Reaction	Acid A	Acid D	Albumin	Sediment	NH_3 Gm	Van Slyke	P H	CO_2 Tension in Mm Hg	Sod Bic, Gm
March													
27		700	1 032	Alk	++	++	+	Trip Phos					
28-29		1,600	1 028	Alk	++	++	Tr	Trip Phos				35 81	
29 30	2,385	1,800	1 012	Alk	++	++	Tr	0		34 77	7 40	35 06	9 3
30 31	2,359	2,170	1 010	Alk	++	++	Tr	0				35 06	9 3
31-1	2,069	2,870	1 007	Alk	+	0	Tr	0					10 0
April													
1 2	2,700	3,150	1 006	Alk	0	0	0	0					9 3
2 3	2,860	3,400	1 008	Alk	0	0	0	0				37 30	10 0
3 4	2,310	2,700	1 010	Alk	0	0	0	0		40 30		35 06	10 0
4 5	3,325	3,250	1 005	Alk	0	0	0	0				30 59	10 0
5 6	2,410	3,500	1 009	Alk	0	0	0	0		42 57			10 0
6 7	3,210	3,720	1 010	Alk	0	0	0	0					10 0
7 8	2,660	2,620	1 006	Alk	0	0	0	0					10 0
8 9	3,520	2,240	1 009	Alk	0	0	0	0					10 0
9 10	2,143	2,200	1 010	Alk	Tr	Tr	0	0		49 05		39 54	23 3
10 11	3,095	2,000	1 014	Alk	Tr	Tr	0	0				41 78	27 0
11 12	2,920	2,240	1 010	Alk	0	0	0	0				41 78	27 0
12 13	3,420	2,600	1 011	Alk	0	0	0	0		43 05	7 50	42 10	27 0
13 14	2,610	2,400	1 011	Alk	F T	0	0	0				50 00	27 0
14 15	3,095	2,300	1 014	Alk	0	0	0	0				44 01	27 0
15 16	2,460	2,680	1 015	Alk	0	0	0	0					27 0
16 17	3,045	2,420	1 012	Alk	0	0	0	0				35 06	5 3
17 18	2,345	3,040	1 005	Alk	0	0	0	0		39 95		26 86*	5 3
18 19	3,110	2,300	1 010	Alk	0	0	0	0				25 36	0
19 20	1 860	3,400	1 010	Alk	0	0	0	0				35 06	
20 21	2,730	3,050	1 007	Alk	0	0	0	0		43 19	7 50	40 28	
21 22	3,420	3,075	1 008	Alk	0	0	0	0				34 32	
22 23	3,180	3,400	1 008	Alk	0	0	0	0					
23 24	3,400	4,000	1 005	Alk	0	0	0	0				38 09	
24-25	3,500	3,700	1 006	Alk	0	0	0	0				34 32	
25-26	3 000	1,370	1 004	Alk	0	0	0	0				39 54	
26-27	3,700	3,620	1 000	Alk	0	0	0	0					
27 28	3,740	3,400	1 005	Acid	0	0	0	0	0 884	41 26		40 28	
28 29	3,510	2,000	1 005	Alk	0	0	0	0				35 32	

P S P First hour 34%
Second hour 12%

46%

* Two determinations made

—IN CASE 5

Sugar Excret % Reduct	Total Sugar Exc, Gm	C H Intake, Gm	Protein Intake, Gm	Fat Intake, Gm	Caloric Intake	Calories per Kg Body Weight	Weight, Kg	C H Bal	Blood Sugar, %	Blood Pressure	Pulse
4 58	32 06	8 00	10 55	17 52	231 88	5 94	38 8	—24 06			85
3 60	57 60	79 67	44 75	46 50	916 18	24 4	37 5	+22 07			85
0 595	10 71	33 74	19 49	19 40	614 12	16 8	37 9	23 03	0 060*	90/74	70
0 360	7 81	25 33	10 03	7 75	211 19	5 5	38 2	17 52	0 375		88
0	0	0	0	0	0	0	8 0	0			90
0	0	0	0	0	0	0	38 1	0			80
0	0	8 96	15 35	13 10	215 98	5 6	38 3	8 96			82
0	0	12 24	26 41	25 40	383 20	10 0	38 3	12 24	0 180		74
0	0	29 48	37 88	42 66	693 38	18 2	38 1	29 48			70
0	0	43 14	59 68	66 02	1,005 46	26 3	38 2	43 14	0 310		73
—0 1	3 72	53 50	66 22	67 11	1,082 87	28 1	38 4	49 78			78
0	0	21 08	16 18	12 01	257 13	6 7	38 4	21 08			86
0	0	30 47	45 72	44 12	701 84	18 8	37 3	30 47			72
—0 1	2 20	50 69	68 71	67 62	1,086 20	28 5	38 1	48 49	0 320		78
0	0	50 71	69 35	68 76	1,099 08	28 2	39 0	50 17			80
0	0	15 88	9 47	9 44	186 36	4 7	39 1	15 88			74
0	0	30 93	65 26	69 84	1,013 23	25 5	39 7	30 93	0 245		70
0	0	64 57	65 50	68 90	1,140 38	28 0	40 6	64 57			68
0 096	2 21	70 74	77 31	78 45	1,298 28	31 9	40 7	68 53			76
0	0	74 98	78 56	78 49	1,320 57	31 9	41 3	74 98			76
S 0 30 B 0 29	7 26	74 98	78 56	78 49	1,320 57	31 3	42 1	67 72			68
0	0	9 55	9 94	16 82	229 34	5 6	40 8	9 55	0 273		74
0	0	36 07	54 79	55 17	859 97	21 9	39 1	36 07		82/70	80
0 17	5 78	55 12	63 06	73 03	1,129 99	29 4	38 4	49 34			80
0 37	11 28	60 13	63 80	63 59	1,068 03	28 3	37 7	48 85	0 224		78
0	0	5 08	14 12	13 86	201 68	5 4	37 3	5 08			92
0	0	30 75	45 44	45 60	715 25	19 4	36 9	30 75			90
0	0	40 13	46 65	42 87	732 95	19 6	37 3	40 13		90/70	74
0 11	4 07	49 27	52 73	53 61	890 49	23 6	37 9	45 20			84
0 103	1 41	49 60	63 40	92 98	1,288 82	34 9	36 9	48 19			80
0	0	14 58	9 38	7 62	164 42	4 5	36 5	14 58			80
0	0	30 47	45 72	44 12	701 84	19 1	36 5	30 47	0 156		78
0	0	45 53	67 79	67 26	1,057 82	28 9	36 6	45 53			66

TABLE 6—Uric Acid, Urea N, Creatin and Diastase in the Cases Tabulated

Case 1				Case 2			
Date	Urea N	Creatin	Diastase	Date	Uric Acid	Urea N	Creatin
3/14/17	14 50	4 20	25 8	1/30/17	3 5	17 63	3 25
3/19/17	16 87	3 35		2/ 9/17		13 25	3 20
3/23/17		4 80		2/19/17			3 70
4/ 3/17		2 40	25 8				
4/ 5/17		4 30					
4/12/17		2 70	27 3				
4/17/17		3 60					
4/20/17	11 13	1 85					

Case 3			Case 4			Case 5			
Date	Urea N	Creatin	Date	Urea N	Creatin	Date	Urea N	Creatin	Diastase
2/ 8/17	11 13	5 44	1/16/17	10 62	3 60	3/29/17			
2/ 9/17		5 35	1/22/17	12 85	3 65	3/30/17	11 62	5 00	
2/10/17		6 00	1/30/17		2 05	4/ 3/17		2 90	
2/13/17	8 38	5 40	2/ 5/17		3 65	4/ 5/17	19 75	4 70	
2/15/17		6 00	2/ 6/17	10 78	3 55	4/ 9/17		3 10	
2/16/17		4 80	2/ 8/17	10 78	3 85	4/12/17	18 50	3 25	75 9
2/20/17	9 50	3 70	2/16/17	10 78	2 60	4/17/17		2 85	
2/23/17	10 00	5 40				4/20/17		2 20	
						4/27/17		3 25	46 80

These studies do not allow deduction to be made in regard to utilization of carbohydrate during the period of gain in weight It would be of interest to determine by calorimeter studies whether there was merely carbohydrate retention or better utilization of carbohydrates From the above deductions in relation to glycosuria, it might be expected that glycosuria would develop during the loss of weight if the carbohydrate had been merely retained The results, however, suggest that a better utilization occurred

Case 3 was not under observation for sufficient time to determine whether there was a change in carbohydrate tolerance Cases 4 and 5 did show a consistent increase of tolerance during the increase of weight This was later decreased as the edema was lost We were unable to state definitely that the sodium bicarbonate, by changing the

acid-base equilibrium, was the responsible cause of this increase Case 5 does show an increased carbohydrate tolerance during the period of bicarbonate ingestion similar to the results reported by Underhill,[17] but we have Case 4 in contrast, which showed this condition, although no bicarbonate was given If such had been the case we would have expected Case 1 to have shown the same result as well as the other cases in this series No edema occurred and the tolerance remained stationary on both bicarbonate and chlorid ingestion

CONCLUSIONS

1 The large amounts of chlorid that diabetic patients will ingest in twenty-four hours is of interest

2 Increase of weight on unrestricted chlorids is invariably associated with their retention The edema usually disappears following the disappearance of glycosuria

3 Soda bicarbonate administration has no constant influence on carbohydrate tolerance in diabetes

4 Cases 4 and 5 show a variation in carbohydrate tolerance, directly in proportion to change in weight, irrespective of whether it is due to chlorid or bicarbonate ingestion

I am greatly indebted to Miss Gertrude Thomas, the hospital dietitian, and to Miss Winifred Swift for technical assistance

THE EGGLESTON METHOD OF ADMINISTERING DIGITALIS

WITH SOME NOTES ON DIGITALIS LUTEA *

S MARX WHITE, M D, AND R EDWIN MORRIS, M D
MINNEAPOLIS

On account of the clinical value of digitalis, the uncertainties in the results and untoward effects after administration have long been the subject of study, especially with a view toward their control or elimination The attempts to secure derivatives, particularly of definite and uniform activity, are too numerous to discuss here The fact that the tincture and the infusion are still more widely used than other preparations shows that the derivatives have not satisfied the demand of physicians Our attempt has been to study these two preparations in such a manner as to control results of therapy by graphic methods, to learn so far as possible the promptitude with which effects can be secured, and the character of such effects

All digitalis preparations used by us have been standardized according to a modification of the cat method of Hatcher In relation to digitalis dosage Eggleston[1] defines the "cat unit" of Hatcher as that amount of the drug calculated per kilogram of cat which is just sufficient to kill when slowly and continuously injected into the vein This is expressed in terms of milligrams of the drug, whether it be in the pure principle or leaf The method employed by one of us (Morris)[2] in standardizing the digitalis preparations is a modification of the Hatcher method similar to that used by Rowntree and Macht[3] Various species of Minnesota digitalis, grown by the Department of Pharmacy of the University of Minnesota, were used

The species *lutea* attracted particular attention, as the first year leaf, grown in Minnesota, ranks in potency with the higher grades of *Digitalis purpurea* In testing *Digitalis lutea* on cats, Morris noticed the lack of irritation and the quiet lethal period, and suggested the use of *Digitalis lutea* in man with the hope of finding a preparation causing less than the usual so-called "gastro-intestinal" irritation As a result

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1 Eggleston Digitalis Dosage, The Archives Int Med, 1915, **16,** 1
2 Morris Journal-Lancet, 1917, **36**
3 Rowntree and Macht Jour Am Med Assn, 1916, **66,** 870

of this suggestion we have studied the action both of the infusion and tincture of *Digitalis lutea* clinically in the wards of the University Hospital The official tincture and infusion of *Digitalis purpurea* and the corresponding preparations from first-year leaves of *Digitalis lutea*, both prepared by the Department of Pharmacy, University of Minnesota, have been used The drugs have been given by one of three methods

1 The method proposed by Eggleston The strength of the preparation to be used is determined in "cat units" and from this the dose for man is calculated The average amount of tincture administered orally required to produce full therapeutic effect (or minor toxic action) and given as above outlined, by the Eggleston method, is about 0 146 c c per pound of patient's body weight (Example Patient weighs 130 pounds, this multiplied by 0 146 equals 18 98 c c Since the infusion is correspondingly weaker in strength, for the infusion give six and two-thirds times this quantity or 126 5 c c) The amount thus determined on is given in four doses within a period of eighteen hours by the following formula The first dose is one-half the total amount to be given, the second, given six hours later, is one half the remainder, and the third and fourth doses, given at six hour intervals, are one half the second dose in amount

2 The method of Eggleston is followed immediately, or after one or two days, by what may be called tonic doses of infusion or tincture, given three or four times daily over a period of days or even weeks These doses are usually 0 6 to 1 c c of the tincture, and 4 to 8 c c of the infusion

3 The tincture or infusion is given in these so-called tonic doses without the previous administration of the larger Eggleston doses

The results of the Eggleston method with or without the later administration of digitalis are of such a character as to warrant report In our studies attention is centered on the records obtained with the polygraph and electrocardiograph, correlated with records and notes of clinical observation

The value of these methods of study should be outlined The polygraph when used in conjunction with the electrocardiograph, as in this study, is principally of value in giving a record of rate and rhythm of arterial and venous pulsations The character of waves recorded by this method is of less value, but even here, since changes in the amplitude, sometimes striking in character, are seen, these changes in amplitude have some value since all records here shown are taken by the same observer with the same instrument [4]

4 Morris' Modifications of the MacKenzie Ink Polygraph, Jour Am Med Assn , 1916, **66,** 1922

The electrocardiograph gives a record with certain features to which particular attention is paid at this time Changes in rate and rhythm are noted as with the polygraph Conduction time, designated P-R (or when a Q-wave is present P-Q) interval, is measured principally in records taken from right arm to left leg (D II)

Changes in conductivity in the junctional tissues (bundle of His and its branches) may occur In cases with auricular fibrillation it is desirable to depress conductivity, this in all probability being the cause of the slowed ventricular rate and remarkable effects during effective digitalis therapy

In the normal nonfibrillating case, slowing by digitalis is due to vagus influences which depress stimulus formation at the sinus node In such cases digitalis may also depress conductivity in the junctional tissues, through both a direct and a vagus action, and this may be shown in two ways

1 A prolongation of conduction time (P-R or P-Q interval) This prolongation may be considerable, as much as 0 25 second, probably even more, before actual blocking of impulses is likely to occur When a prolongation of conduction time beyond 0 2 second is found before administering digitalis, the drug must be used very cautiously, if at all, and then only in the presence of very distinct indications When a normal conduction time (less than 0 2 second) before giving digitalis, gives way to a prolongation after digitalis, the same caution should be observed In both instances the electrocardiogram provides the best if not the only effective means of study and control

2 Partial or complete block (Auriculoventricular disassociation) If depression in conductivity with increase in conduction time becomes too great, slowing because of missed beats, or of an idioventricular rhythm, occurs This cannot aid cardiac action, and should be rigidly guarded against wherever possible The well known effect of atropin in removing a digitalis block is evanescent and requires too much of the drug to be a comfortable safeguard

A still further effect of digitalis on the heart is the production of extrasystoles through increase of irritability in the myocardium, particularly of the ventricles When this occurs the well known paired beats may be seen, each pair due to a contraction of the normal supraventricular type, followed by a ventricular extrasystole, and this by a compensatory pause Extrasystoles often occur before digitalis is given, but when so frequent as to give paired beats, a digitalis influence is probable, and when pairing occurs in a case of auricular fibrillation, is certain

It has been established by many observers that in the electrocardiogram the normal ventricular complex (Q, R, S, and T waves) remains

constant in outline in any healthy person This is true also for individuals with diseased hearts in whom the condition of the heart remains unchanged Unless alterations occur in the heart, the ventricular complex for any individual remains unchanged through life So true is this that where repeated tracings from one individual have been taken, identification may often be made from an electrocardiogram

Comparison of the electrocardiograms taken from the same individual when free from digitalis effects and when under the influence of digitalis may show changes in conduction time and in outline of the complexes, as well as change in the rate and rhythm Lewis[5] says

> The duration of the normal P-R interval as measured in Lead II may vary from 0 13 to 0 21 second It usually lies between 0 13 and 0 16 second A P-R interval of 0 16 second and accompanying heart rates of 90 and over is probably of pathologic duration A P-R interval of 0 20 second and over is probably of pathologic duration in all but exceptional instances, whatever the heart rate may be which it accompanies

Referring to the T-wave, Lewis[5] says

> T is always an upward variation in Lead II It may show partial inversion in Lead I on rare occasions, partial or complete inversion in Lead III is relatively common, and occurs especially in association with splintering of the curves during the opening phases of ventricular systole

The most valuable and extensive contribution on the modifications in the electrocardiogram produced by digitalis is by Cohn, Fraser and Jamieson[6] They assert that in curves of patients under treatment with digitalis, alterations in the T waves of the electrocardiograms occurred in a large number (thirty times in thirty-four patients), and that the change was detected before alteration in rhythm or conduction time had occurred and before symptoms referable to the gastro-intestinal tract disturbed the patients (except in five instances) Other changes in the ventricular complex were noted They say that an alteration in the curve may be taken as evidence that the influence of digitalis is being exerted on the heart, and that changes in the T-waves were detected after an equivalent of 1 2 gm or even less of the dried leaves of digitalis were given, that is to say, on the third day of administration, on several occasions they show the altered forms after thirty-six to forty-eight hours

Clinical observation comprises a study of features familiar to all Eggleston[1] describes the principal points in clinical improvement as slowing in pulse and respiration rates, the more or less rapid subsidence of dyspnea, orthopnea, and persistent cough, and clearing of lung bases, in fibrillation, decrease in pulse deficit, the clearing of congested liver and splanchnic region with loss of pulsation and tenderness, and

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5 Lewis Philosoph Trans, Royal Soc, London, Series B, 1912 **202.**
6 Cohn, Fraser and Jamieson Jour Exper Med, 1915, **21,** 593

diminution in size, the diminution in cyanosis, improvement of cold extremities, the disappearance of edema and increase in urinary output

In cases of auricular fibrillation records are shown of simultaneous apical and radial rates, illustrating the so-called pulse deficit and the changes in the rate and deficit under digitalis

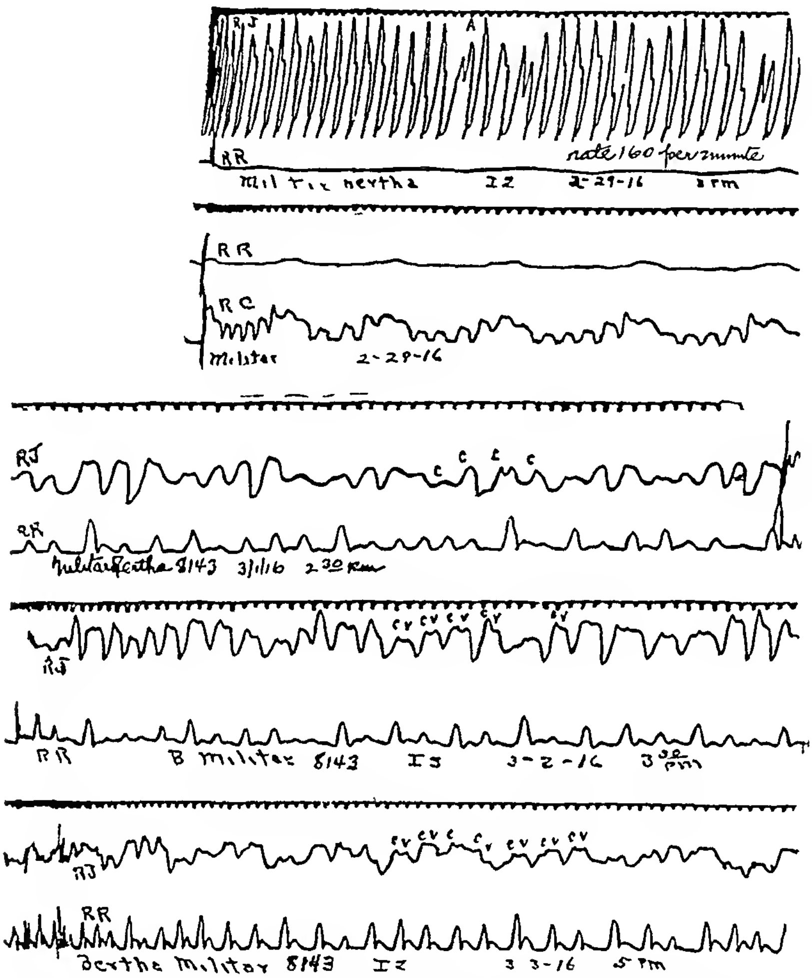

Fig 1—(Case 1) Polygrams, Feb 29, 1916, from right radial (R R) right jugular (R J) and right Carotid (R C) Radial pulse almost imperceptible but shows expiratory filling and expiratory collapse Carotid shows large, and jugular, enormous, waves, total arrhythmia March 1, March 2 and March 3, 1916, show successive increase in radial, and decrease in jugular pulse waves, with distinct effect within twenty-four hours

REPORT OF CASES

Case 1—B M, woman, aged 32 (Hosp No 8143), was admitted Feb 28, 1916 Clinical diagnoses (1) chronic valvular disease of heart and mitral regurgitation, (2) chronic myocardial degeneration with decompensation, (3) auricular fibrillation, (4) passive congestion of viscera, (5) ascites and anasarca

Weight not determined on admission, a very small woman estimated to weigh about 120 pounds, with tremendous amounts of fluid in tissues and peritoneum

Digitalis was given as follows

Feb 29, 1916 Infusion digitalis 45 c c

March 1, 1916 Infusion digitalis 15 c c (total 60 c c in eighteen hours, one-half Eggleston dosage given because of fluid)

March 2, 1916 Infusion digitalis 75 c c

March 3, 1916 Infusion digitalis 15 c c (total 90 c c in eighteen hours, three-fourths Eggleston dosage, following half Eggleston dosage of preceding two days)

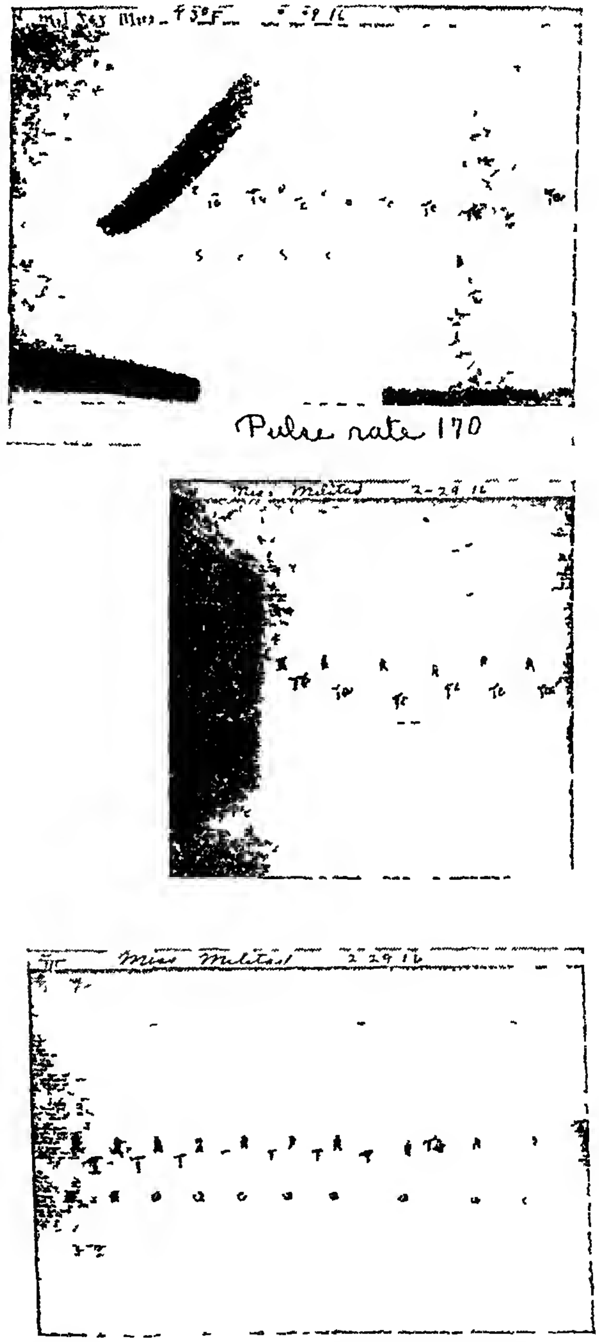

Fig 2—(Case 1) Feb 29, 1916, auricular fibrillation, pulse rate 170, total arrhythmia T-wave positive in D I and D II, slightly inverted in D III, but varies in outline probably because of the deflections of galvanometer string due to the auricular fibrillation

Then 45 c c infusion were given daily except for short periods following toxic symptoms

Polygrams Feb 29, 1916, March 1, 1916, March 2, 1916, and March 3, 1916 (Fig 1), show total arrhythmia (auricular fibrillation) and marked improvement in radial pulse, with lessening of excessive pulsation in jugulars and carotids

Feb 29, 1916 Electrocardiogram (Fig 2) (before digitalis was given) T positive in D I and D II, inverted in D III Pulse rate average 170 Auricular fibrillation

March 1, 1916 Electrocardiogram (Fig 3) T positive in D I and inverted in D II and III Pulse rate 155 (General condition considerably improved)

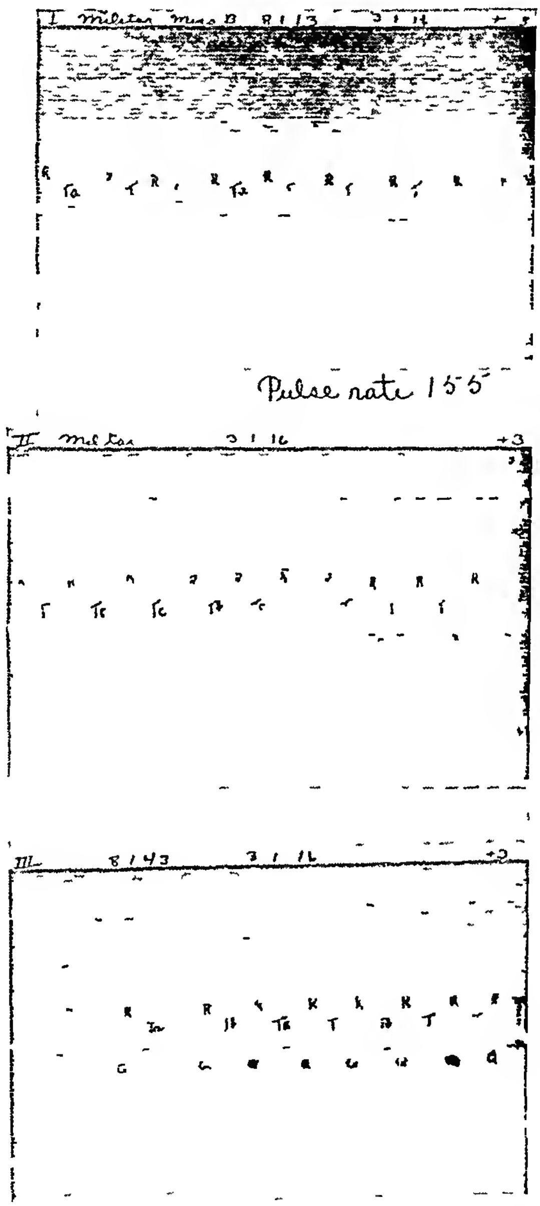

Fig 3—(Case 1) March 1, 1916, auricular fibrillation continues, pulse rate 155 T-wave positive in D I and inverted in D II and D III

March 2, 1916 Electrocardiogram (Fig 4) Tracings similar to March 1, 1916 Pulse rate average, 130 (Patient shows marked improvement clinically)

March 8, 1916 Electrocardiogram (Fig 5) T shows distinct inversion in D I, D II and D III Pulse rate average 90

In this case, one of auricular fibrillation with alarming decompensation, the digitalis effect was very apparent in less than twenty-four hours, and within forty-eight hours after beginning the drug, the

patient was feeling so much better that she wanted to get up and about The change in the T-wave is only moderate in degree and develops rather slowly, although it is apparent within twenty-four hours after beginning digitalis therapy The reduction in pulse rate, probably through blocking the less effective impulses through the bundle of His, is striking

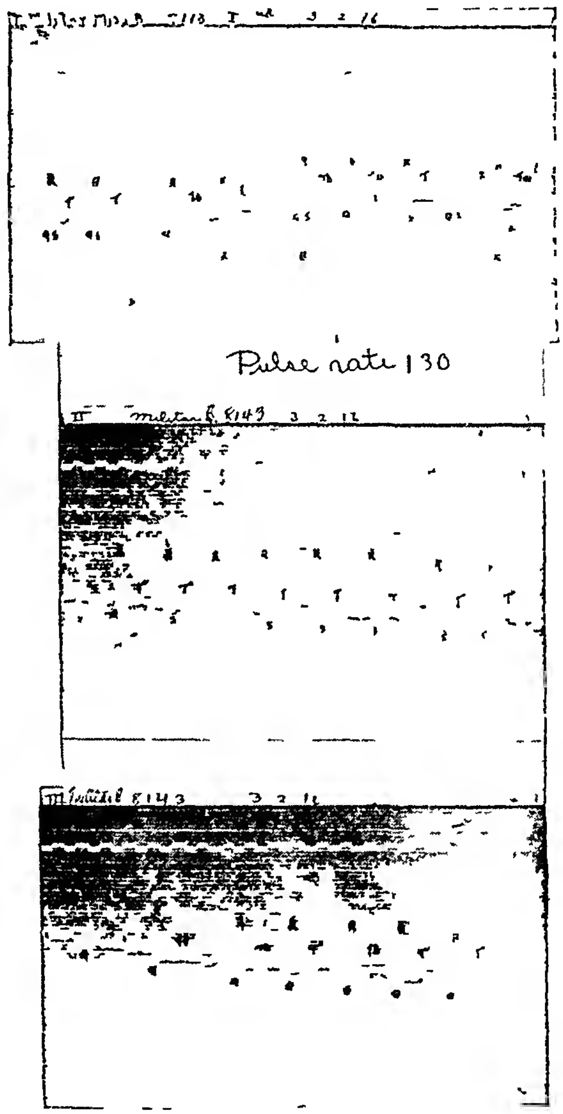

Fig 4—(Case 1) March 2, 1916, tracing shows pulse irregular, rate averaging 130, with T-wave showing little if any change from previous day

An intercurrent erysipelas of the thigh developed March 12, subsiding within ten days

Later, after prolonged rest and digitalis therapy, the patient developed regular pulse with P-waves shown in electrocardiograms This occurred after at least six months of auricular fibrillation Later, the patient developed pericarditis and died Oct 14, 1916, seven and one-half months after this study

Necropsy diagnoses 1 Advanced chronic and acute serofibrino hemorrhagic pericarditis 2 Acute myocarditis (myomalacia cordis) 3 Dilatation of heart 4 Chronic passive congestion of liver, spleen and kidneys 5 Mild acute parenchymatous nephritis

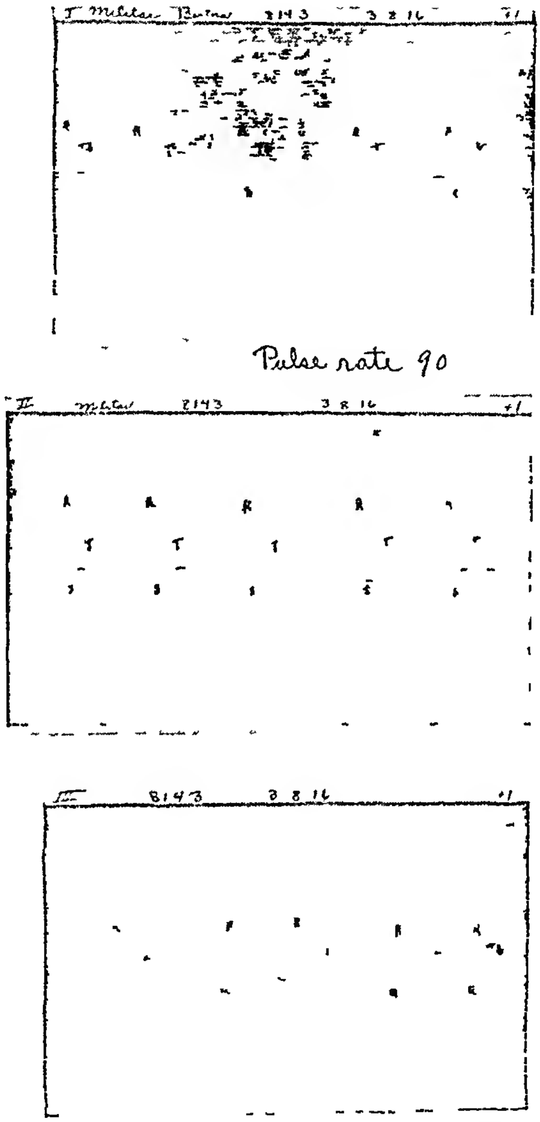

Fig 5—(Case 1) March 8, 1917, marked slowing, rate 90, irregular, with the small deflections and auricular fibrillation T-wave inverted in D I, D II and D III

Case 2—F F, man, aged 30 (Hosp No 8669)

Clinical diagnoses (1) mitral and aortic insufficiency, (2) exophthalmic goiter, (3) auricular fibrillation, (4) chronic amygdalitis, (5) alveolar abscesses, pyorrhea alveolaris

Digitalis was given as follows

May 10, 1916 Infusion digitalis 142 5 c c (4¾ ounces)

May 11, 1916 Infusion digitalis 52 5 c c (1¾ ounces)

(The foregoing constituting for this patient the calculated "Eggleston dosage")

May 15, 1916 Infusion digitalis 187 5 c c (6¼ ounces), "Eggleston dosage"
May 31, 1916 Infusion digitalis 60 c c (2 ounces)
June 1, 1916 Infusion digitalis 60 c c (2 ounces)

May 10, 1916, and May 11, 1916 (Fig 6), four polygrams showing marked improvement in rate and character of pulse, May 10 shows rate 163 per minute, May 11 shows rate 98 per minute, total arrhythmia, due to auricular fibrillation

May 14, 1916, May 15, 1916, and May 16, 1916 (Fig 7), five polygrams show total arrhythmia The two lower tracings, which are continuous, show onset and offset of a period of "paired" beats which developed next day, May 16, 1916, after the second Eggleston dose

May 17, 1916 Electrocardiogram (Fig 8) Auricular fibrillation T isoelectric in D I, negative 1 mm in D II Paired beats, each pair consisting of a normal supraventricular type of complex followed by a ventricular extrasystole

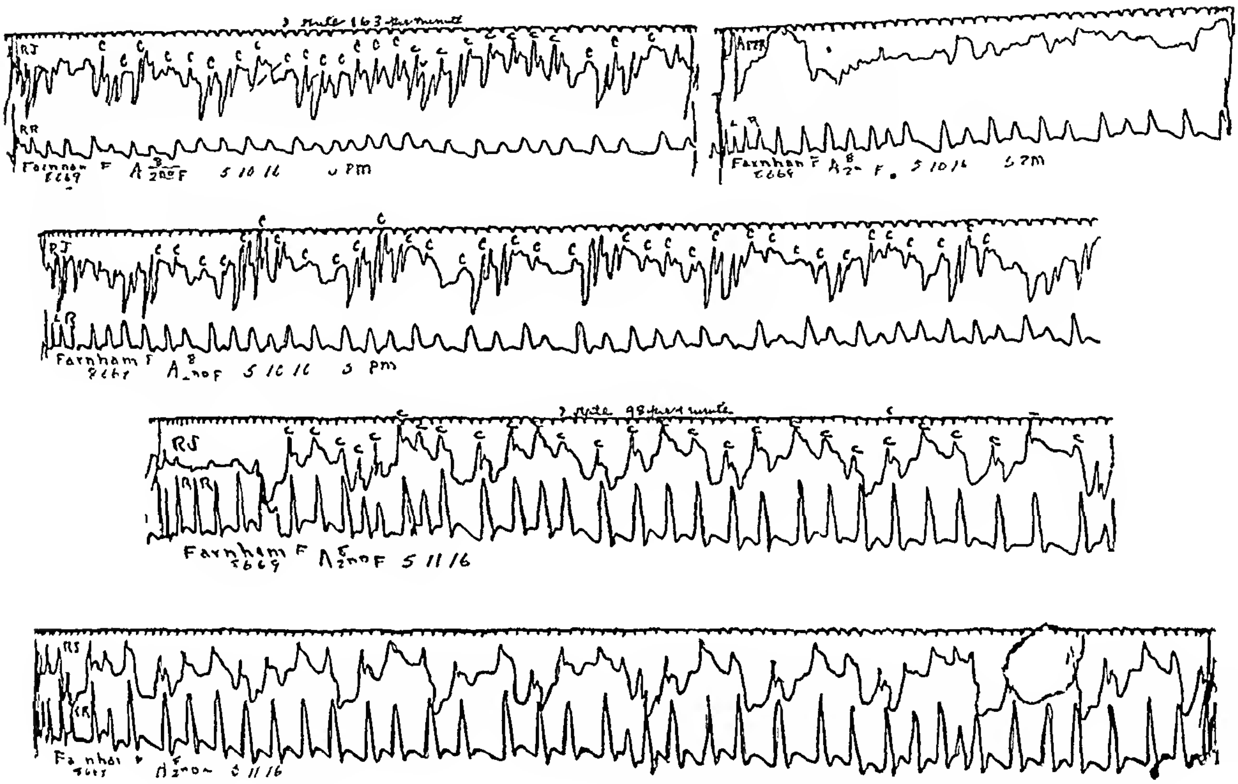

Fig 6—(Case 2) Polygrams, May 10, 1916, right jugular (R J) and right radial (R R), apex and left radial (L R), and right jugular (R J) and left radial (L R) show small radial and large jugular pulsations Rate 163, total arrhythmia, due to auricular fibrillation May 11, 1916, shows marked lessening of jugular and increase in radial pulse wave, with development of pulsus celer type of wave Total arrhythmia, rate 98

June 21, 1916 Electrocardiogram (Fig 9) (No digitalis for twenty days) Auricular fibrillation Rate increased to 120 per minute T positive in D I and D II, slightly negative, then positive in D III

July 12, 1916 Electrocardiogram (Fig 10) (no digitalis for forty-one days) Auricular fibrillation, ventricular rate 153 per minute, T a distinct positive wave in D I, D II and D III

In this patient, the pulse rate showed a deficit, between apical and radial, varying from 8 beats to 36 per minute May 15, after the second Eggleston dosage, the apical rate, which had been between 118 and 140, dropped to 104 within twelve hours and remained at or below

this point for thirty-six hours longer, gradually rising again to a maximum of 154 on May 19 Marked clinical improvement with increase of urinary output while on a constant diet and fluid intake accompanied the slowing of rate, as shown by totals of twenty-four hour urines as follows

May 12, 250 c c , May 13, 250 c c , May 14, 300 c c , May 15, 550 c c , May 16, 425 c c , May 17, 400 c c , May 18, 325 c c , May 19, 200 c c

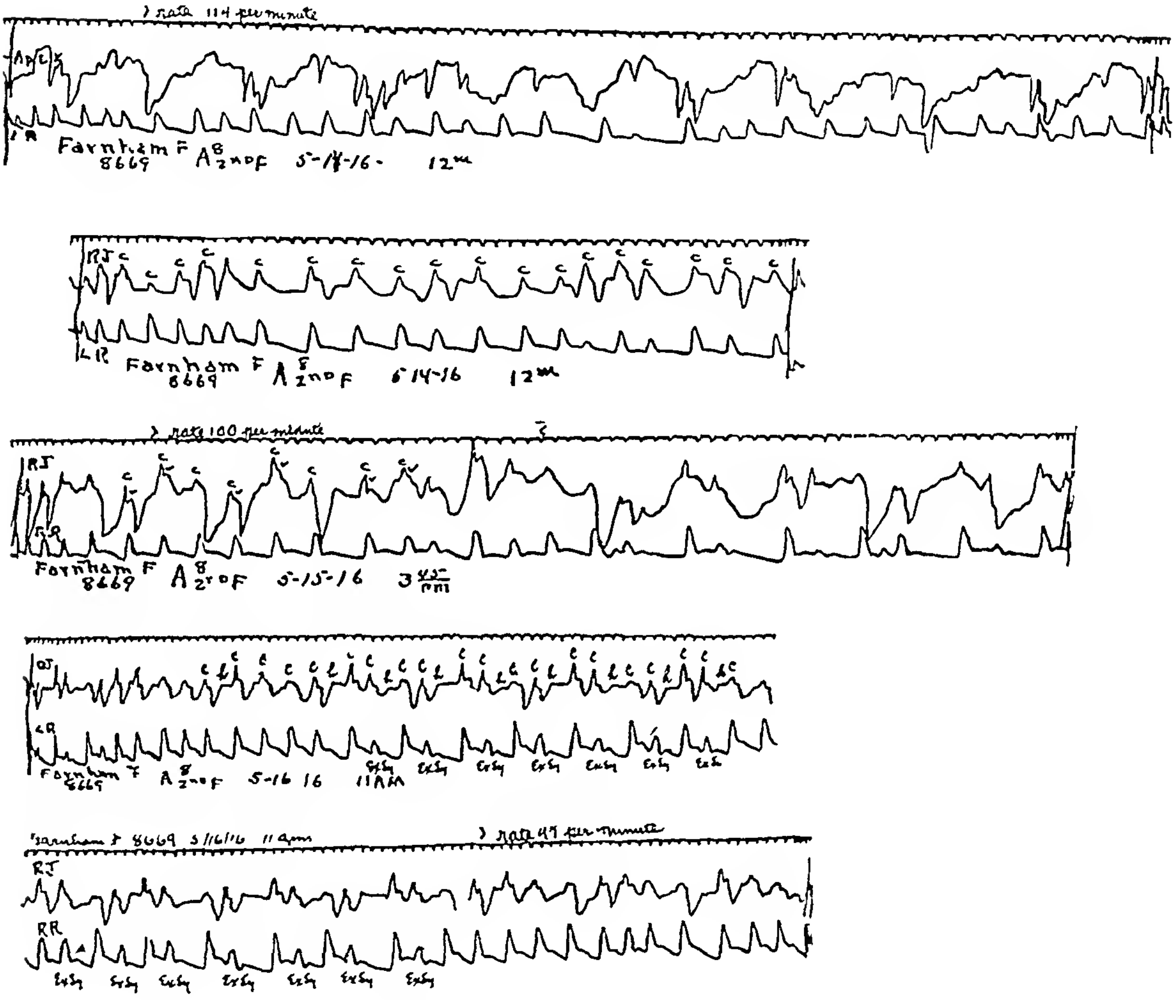

Fig 7—(Case 2) Polygrams, May 14, 1916, show total arrhythmia, rate 114 (Apex and left radial, and right jugular and left radial) May 15, 1916, shows same arrhythmia, rate 100 per minute May 16, 1916, the two lower tracings, which are continuous, show the onset and offset of a short period of paired beats, every second (smaller) beat an extrasystole The fundamental arrhythmia is apparent even during this period

There is not only marked and prompt improvement in this case, with the reduction in pulse rate and changes in T-wave within twenty-four hours, but after the second Eggleston dose, following the first by only four days, the appearance of extrasystoles shows the irritant action of digitalis on the ventricles, indicating overdosage This lasted

five days, then disappeared Fortunately there seemed to be no interference with the patient's clinical improvement A digitalis effect is shown twenty days after the last dose

The patient refused to take even ordinary precautions after leaving hospital and died suddenly at home about three months later

CASE 3—Mrs J P, aged 48 (Hosp No 10034), was admitted Nov 17, 1916, discharged Jan 17, 1917

Clinical diagnoses (1) chronic myocarditis with auricular fibrillation, (2) aortic and mitral insufficiency, (3) edema of lungs, (4) anasarca, (5) chronic amygdalitis

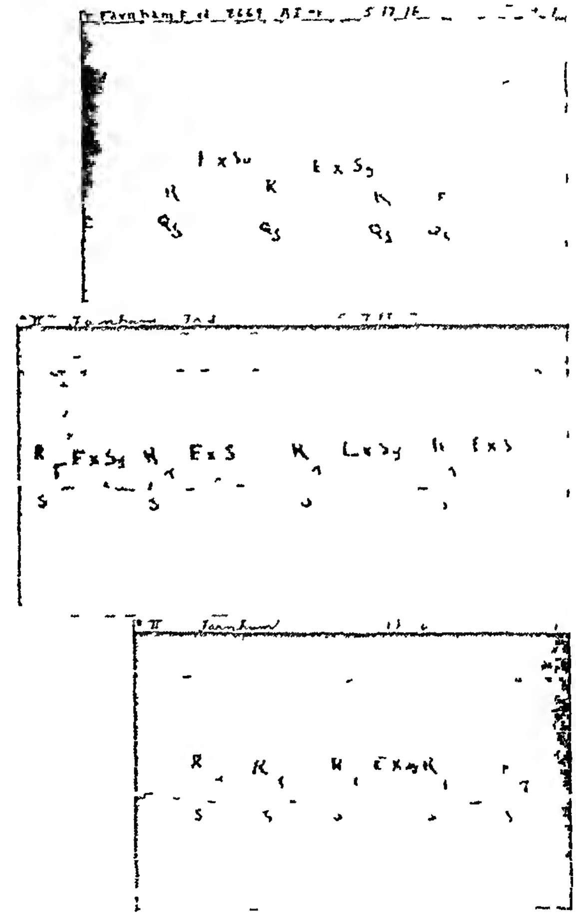

Fig 8—(Case 2) Auricular fibrillation T is iso-electric in D I, inverted in D II (two lower strips) Paired beats, due to regularly recurring ventricular extrasystoles

Weight, 135 pounds The patient was given infusion *Digitalis lutea* Nov 18, 1916, and Nov 19, 1916, 130 c c, "Eggleston dosage"

Nov 18, 1916 Electrocardiogram (Fig 11) Auricular fibrillation T shows slight inversion in D I, slight inversion and then positive in D II, slightly positive in D III, pulse rate 96

Nov 20, 1916 Electrocardiogram (Fig 12) Auricular fibrillation Inversion T-wave in D I and D II, pulse rate 70

Nov 21, 1916 Electrocardiogram (Fig 13) Auricular fibrillation T-wave shows still greater inversion, pairing of beats, shown only in D III, pulse rate 55

Nov 24, 1916 Pulse rate 55, and by Dec 19, 1916, the pulse rate was back to 95, at which time the electrocardiographic tracing shows ventricular complex free from digitalis influence, with T upright

Within the twenty-four hours following the first dose of *Digitalis lutea,* a tremendous output of urine began, 2,700 c c (900 c c intake) with 1,800 c c output (600 c c intake) the next day, the output remaining more than the intake for eight days, while after this time

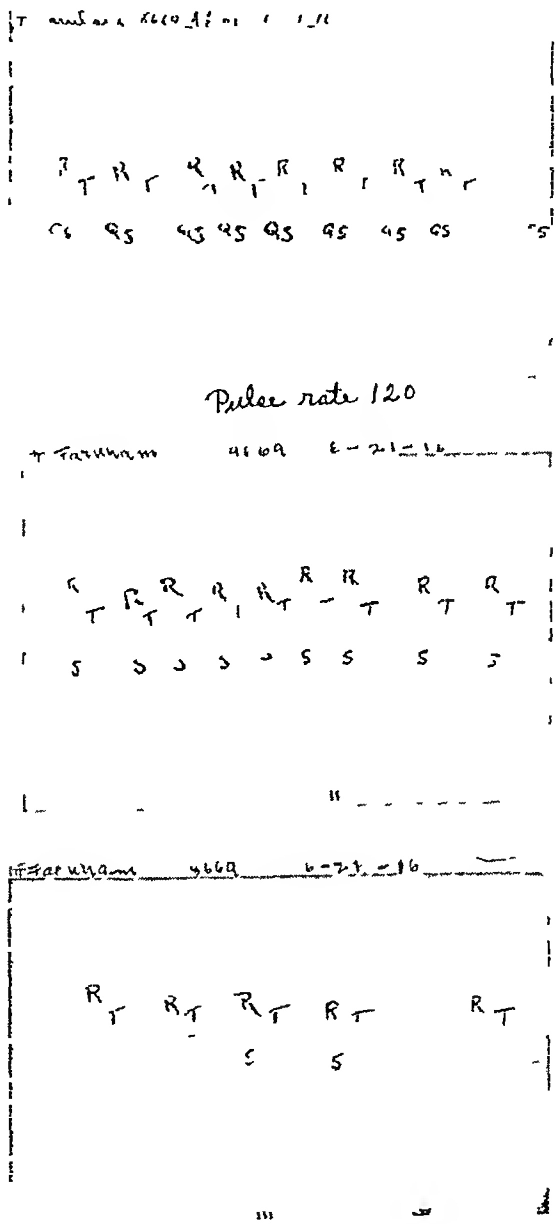

Fig 9—(Case 2) (No digitalis for fourteen days) shows fibrillation of auricles, with increase in rate of ventricles, and disappearance of paired beats, with change in T-wave toward the digitalis-free type (See Fig 10)

the intake constantly exceeded output Clinical improvement was marked, and began within twenty-four hours after beginning the drug That this patient had had some digitalis before entering the hospital cannot be excluded It is suggested by the rate 96, and by moderate

inversion of T-wave before beginning the drug It was not enough, however, and distinct improvement followed effective administration Increased irritability of ventricle, as shown by paired beats (D III, Fig 13), showed not until nearly forty-eight hours after suspending the drug There was no apparent ill effect from it.

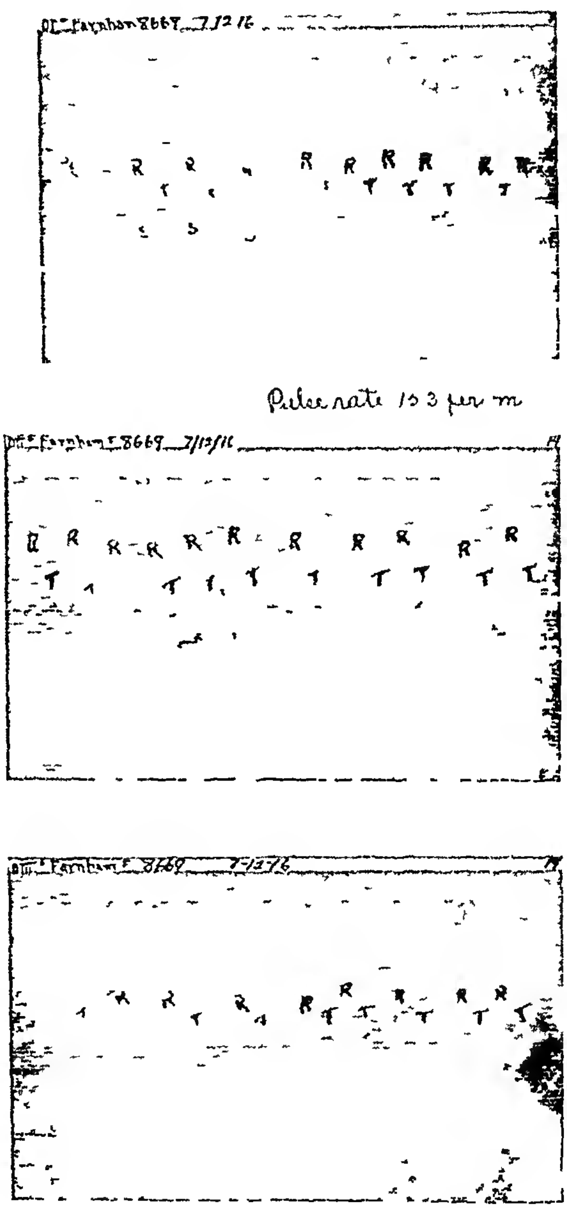

Fig 10—(Case 2) (No digitalis for forty-one days) Ventricular rate has increased again almost to the figures before digitalis was used (Compare first tracing in Fig 6 polygram) T-wave again distinctly upright, though modified frequently by deflections caused by auricular fibrillation

Case 4—Mrs A R, aged 39 (Hosp No 10881), was admitted March 20, 1917, discharged May 22, 1917

Clinical diagnoses (1) goiter, (2) chronic valvular disease of heart with mitral insufficiency, and decompensation, (3) auricular fibrillation, (4) passive congestion of viscera, (5) ascites and anasarca, (6) chronic amygdalitis

Weight 96 pounds The patient received tincture *Digitalis lutea* 14 c c in eighteen hours ("Eggleston dosage") March 24, 1917, and March 25, 1917

The electrocardiogram shows auricular fibrillation with inversion of T-wave and slowing of rate from 130, March 24, 1917, to 80, March 26, 1917

The chart (Fig 14) shows reduction of pulse deficit, with marked reduction of rate as taken at the apex, but little change in rate as taken at the radial The apical rate is permanently below its former level within sixteen hours after the first dose

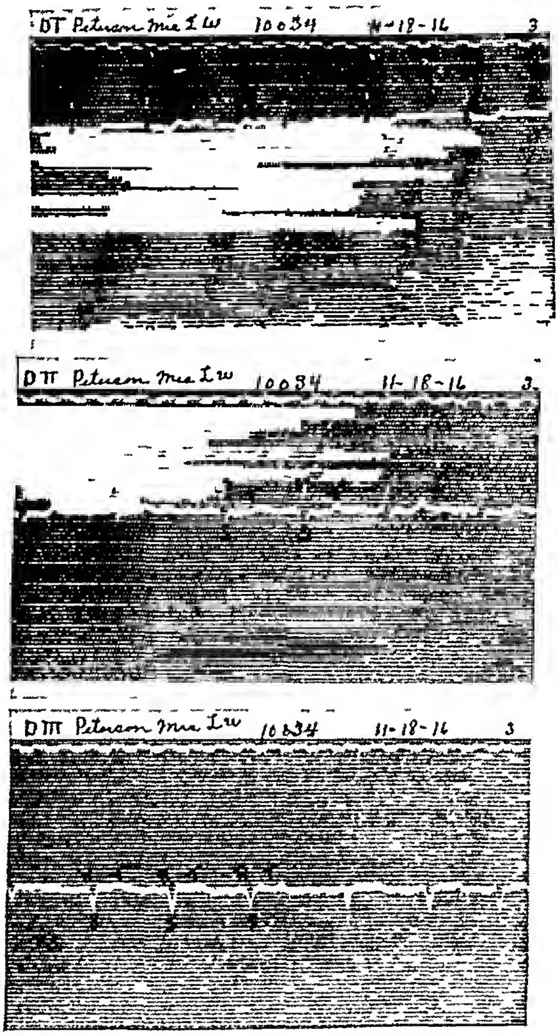

Fig 11—(Case 3) Auricular fibrillation, pulse rate 96, with inversion of first portion of T-wave in D I and D II, suggests some digitalis effect Note increasing inversion after Eggleston method (see Fig 12)

A chart (Fig 15), giving intake and output of fluids with a study of sodium chlorid output in urine and stools while on a diet with known constant salt intake and a daily purgative dose of Epsom salts, shows marked increase in fluid and sodium chlorid output immediately following the drug We are indebted to Dr Floyd E Grave, in charge of the chemical laboratory, Department of Medicine, for this study The patient showed marked clinical improvement

CASE 5—Mrs L M, aged 49 (Hosp No 10904), was admitted March 24, 1917, discharged May 19, 1917

Clinical diagnoses (1) chronic valvular disease of heart with mitral insufficiency, (2) myocardial degeneration with auricular fibrillation, (3) hypertrophy and dilatation of heart, (4) chronic passive congestion of viscera, (5) infarct of lung, (6) ascites, (7) chronic amygdalitis, (8) dental caries

The patient received infusion *Digitalis lutea*, 60 c c March 24, 1917 (three-fourths Eggleston dosage)

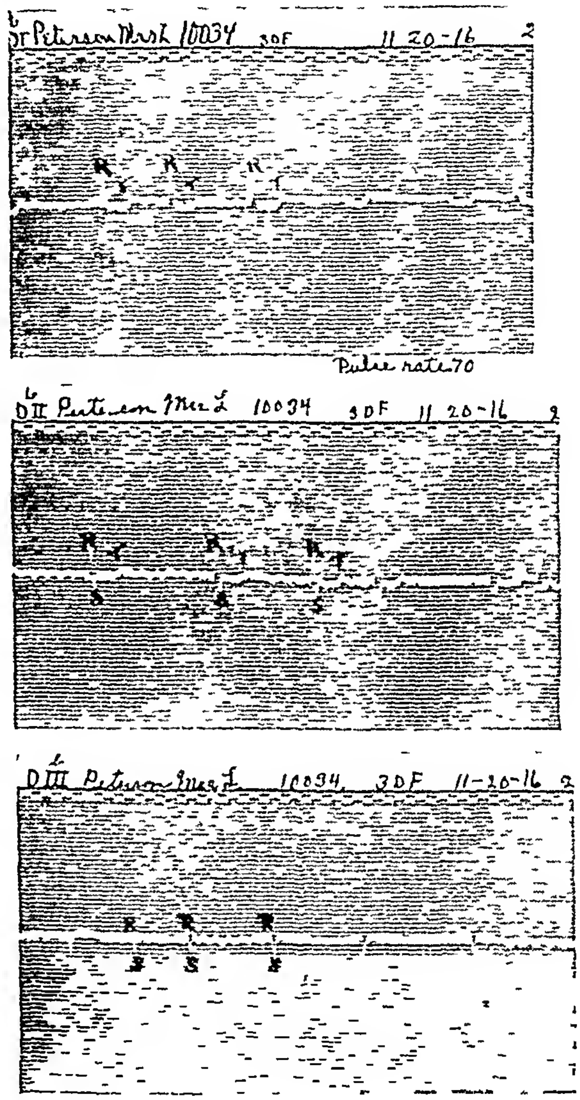

Fig 12—(Case 3) Fibrillation continues, pulse rate 70, slower within thirty-six hours, and T-wave shows marked inversion in D I and D II

Electrocardiographic tracings show inversion of T-wave in twenty-four hours after administration of digitalis

Pulse chart (Fig 16) shows striking reduction of pulse deficit and slowing of both apical and radial rates within eighteen hours after beginning digitalis There was some amelioration of symptoms but no decided clinical improvement at first

Fluid charts could not be made because of a pronounced psychosis

Karell diet, complete rest, and digitalis in "tonic" doses, gradually brought about improvement, and at the time of leaving the hospital no evidences of decompensation could be found

Case 6—G D M, man, aged 55

Clinical diagnoses (1) simple goiter (large), (2) mitral insufficiency (mild grade), (3) myocarditis (moderate grade), (4) paroxysmal auricular flutter

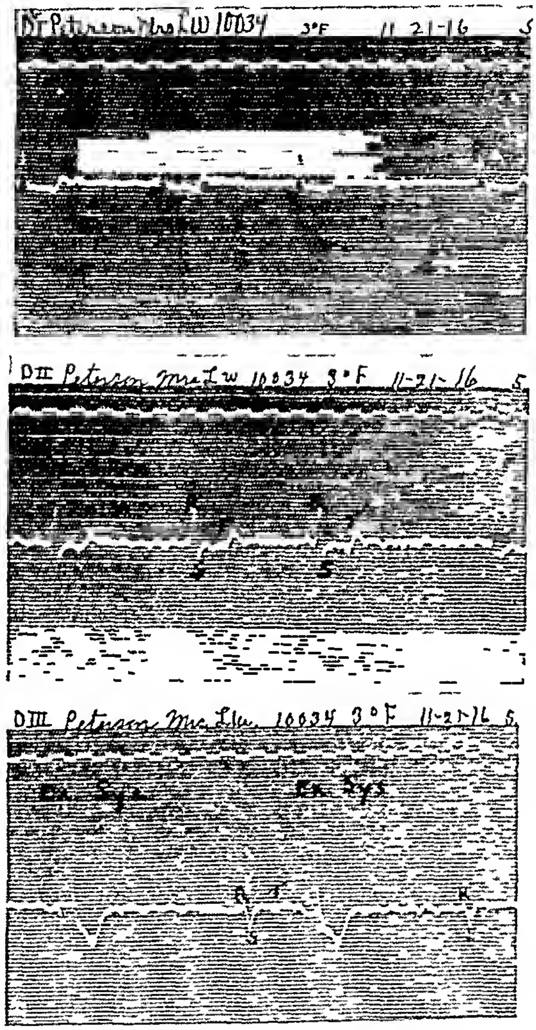

Fig 13—(Case 3) Pulse rate 55 Auricular fibrillation of very coarse type T shows marked inversion In D III frequent ventricular extrasystoles cause paired beats

For about eight months the patient had occasional attacks of "palpitation" of the heart, coming on usually after dinner in the evening, but occasionally after overexertion There was no precordial pain During the attack he became somewhat dyspneic and the attacks lasted from a few minutes to one-half hour

Digitalis was taken as follows infusion digitalis, 150 c c in twenty-four hours (Eggleston method) beginning Sept 19, 1916, followed by same infusion 90 c c daily until Sept 23, 1916

Sept 14, 1916 Electrocardiogram (had no digitalis) Tracing taken during attack of auricular flutter Auricular rate 324 per minute, ventricular rate 162 per minute

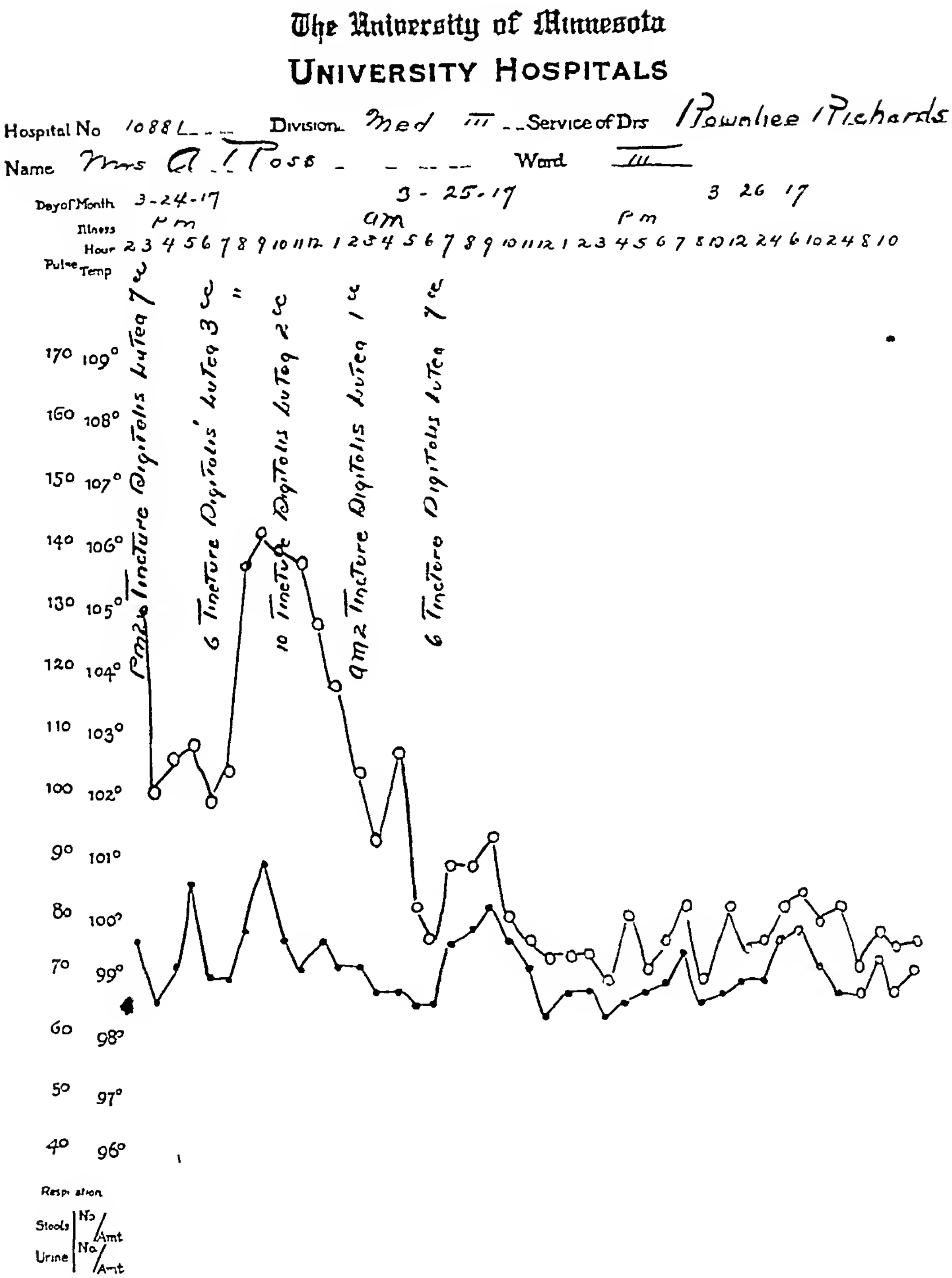

Fig 14—(Case 4) Pulse chart showing rates taken at heart apex (upper lines joining circles) and at radial (lower lines joining dots) The deficit decreases by reduction in apical rate The radial rate remains stationary and if this alone were studied false conclusions regarding digitalis effect on heart rate would be drawn

Sept 19, 1916 Electrocardiogram (before beginning digitalis) P-Q interval 0 15 second in D II Positive in all derivations

Sept 21, 1916 Electrocardiogram (took infusion digitalis 150 c c Sept 19 and 20) P-Q interval 0 16 second in D II Definite flattening of T-waves in all derivations

The patient appeared at the clinic Sept 23, 1916, during a paroxysm, undoubtedly of auricular flutter The pulse rate was 160 and perfectly regular as felt at the wrist He was taken to electrocardiographic station, but by the time the apparatus was adjusted the rapid, regular rate had disappeared and been replaced by absolute arrhythmia A polygram taken at 9 45 a m shows absolute arrhythmia, rate 110 per minute A polygram taken at 9 55 a m shows rate 130, perfectly regular A good jugular tracing could not be obtained A tracing taken Sept 25, 1916, two days later, shows regular rhythm, with good jugular waves (normal condition)

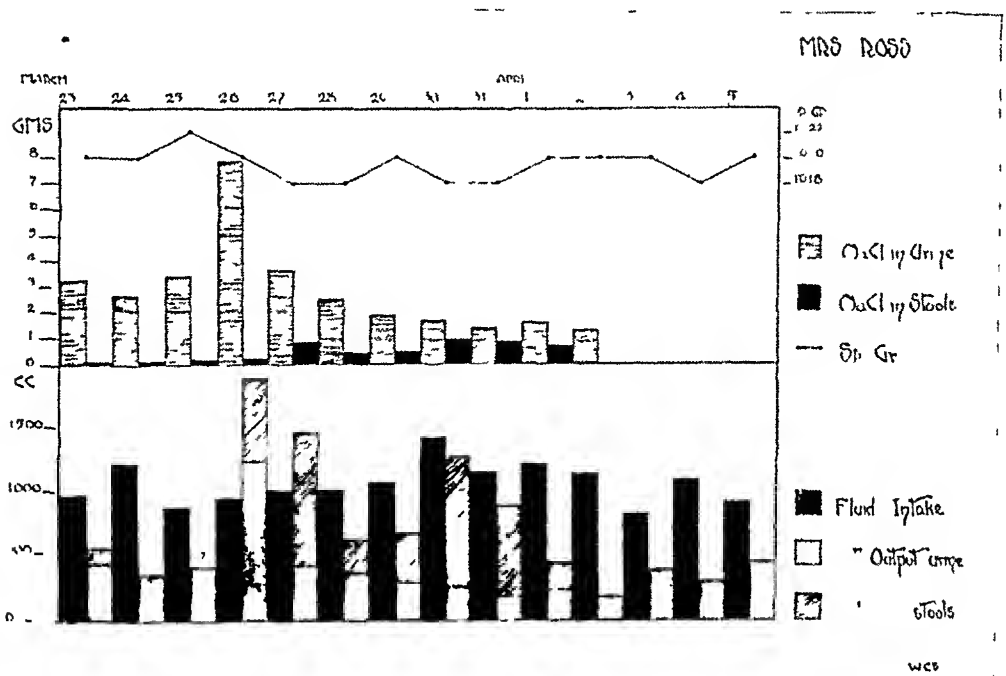

Fig 15—(Case 4) Showing intake of fluids and output of sodium chlorid in urine and stools March 24 and 25, the amount of fluid in stools was not accurately measured, but there was no radical error as shown by the amounts of sodium chlorid recovered (Middle chart)

Sept 23, 1916 Electrocardiogram, taken at 9 40-41-42 a m, presenting auricular fibrillation during subsidence of flutter, shows a rate of 110 with absolute arrhythmia In D I, T is much flattened, T-wave inverted in D II and D III

Sept 23, 1916 Electrocardiogram taken at 9 50-51-52 a m shows a normal sequence of auricular and ventricular complexes ten minutes after Figure 21 was taken T is flattened in D I inverted in D II and D III, P-Q interval 0 16 second in D II, one extrasystole shown in D I

Sept 25, 1916 Electrocardiogram (still taking digitalis in "tonic" doses) T is inverted during first portion then slightly positive in D I, more marked inversion of T than formerly in D II and D III

This patient had considerable nausea after ten days on infusion of digitalis He was later given *Digitalis lutea* in larger doses than for-

merly, with no nausea The use of digitalis lessened the frequency and shortened the duration of the paroxysms Later, after thyroidectomy, the paroxysms remained absent for six months and the patient

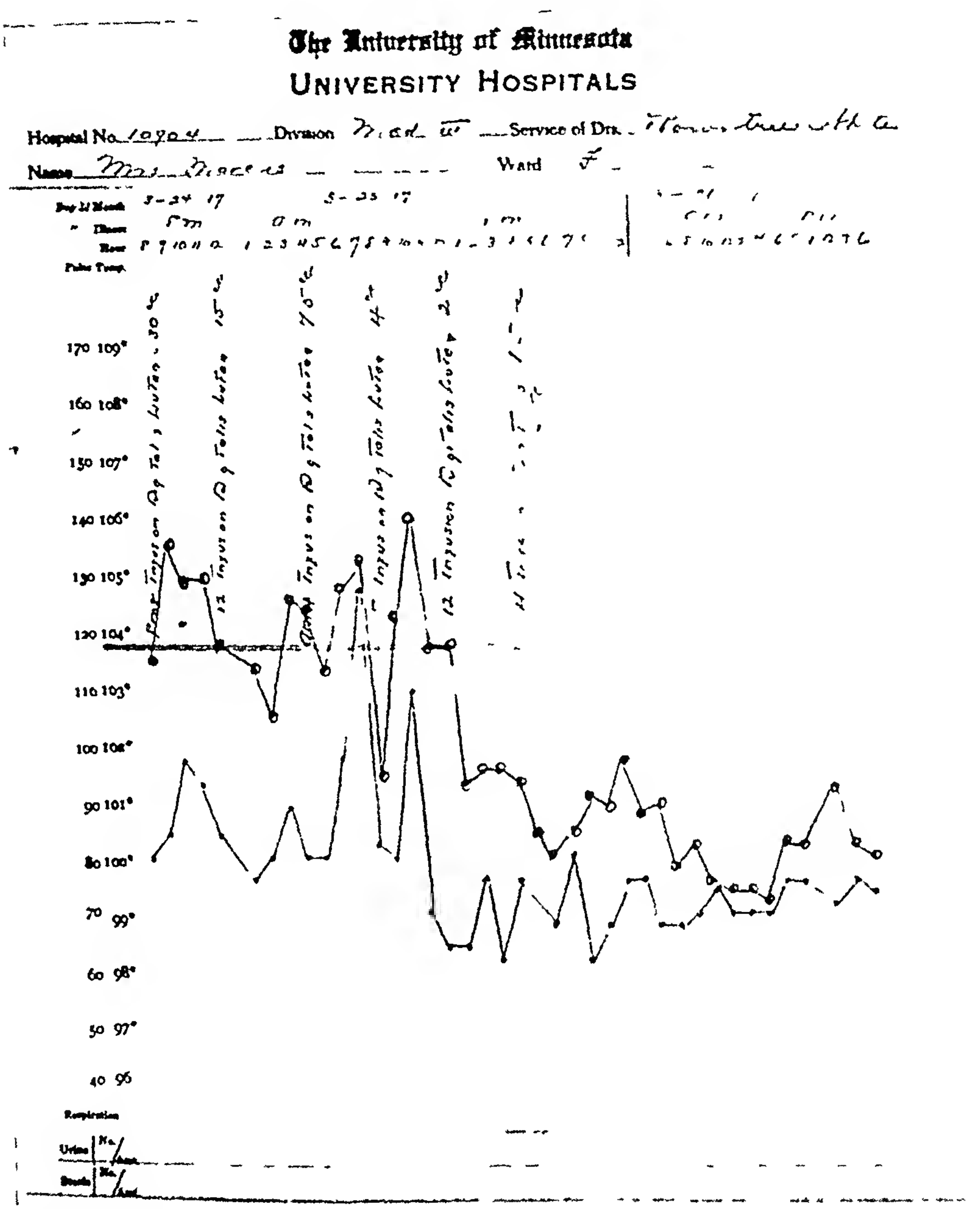

Fig 16—(Case 5) Pulse chart showing decrease in rate and deficit, with prompt digitalis effect in eighteen hours In this case the deficit, early, sometimes decreased in part by improvement in character of radial pulse

was able to do full work This case is reported in greater detail and with tracings in a short paper by us on "Paroxysmal Auricular Flutter"

Case 7—John M, man, aged 32 (Hosp No 8256), was admitted March 16, 1916, discharged June 15, 1916

Clinical diagnoses (1) exophthalmic goiter, a case of moderate severity, with

enlarged thyroid, (2) nervousness, tremor, weakness, exophthalmos, tachycardia with regular pulse, and a blowing systolic murmur (probably functional) over the mitral area

Weight 165 pounds The patient was given infusion digitalis May 2, 1916, 165 c c (Eggleston dosage), followed by 90 c c May 3

May 2, 1916 Electrocardiogram before digitalis was given The pulse rate was 135 per minute while at heart station, when quiet in bed the chart shows 100 to 105 T positive in D I, D II and D III

May 5, 1916 Electrocardiogram T inverted, then slightly positive in D I, inverted and slightly positive in D II, inverted D III

May 9, 1916 Electrocardiogram T inverted and positive in D I, inverted, then slightly positive in D II, inverted in D III

The pulse rate slowed from 100 and 105 before digitalis to 90 and 95 after digitalis and remained so for two weeks, then returned to 105 and 110 per minute, coincident with return of the T-wave to its normal upright form The principal evidence of digitalis effect in this case is in the moderate slowing of pulse rate and in the change in T-wave This effect is apparent at least six days after withdrawing the drug No change in conduction time is found

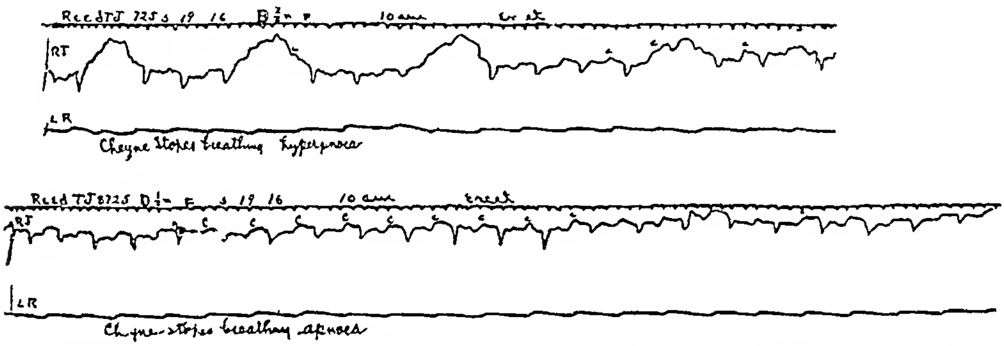

Fig 17—(Case 10) Polygrams May 19, 1916 (before digitalis was given) Impossible to get good radial or jugular tracings, pulse barely perceptible with finger Shows period of hyperpnea, and of apnea, respectively, in Cheyne-Stokes breathing (Compare with Fig 18)

Case 8—Mrs A L, aged 26 (Hosp No 9861)

Clinical diagnoses (1) retroversion of uterus, (2) enlarged thyroid, (3) pyorrhea alveolaris

Weight, 110 pounds The patient received infusion *Digitalis lutea,* 108 c c (Eggleston method) Nov 5, 1916, then 3 c c daily (min 45) Nov 7, 1916, to Nov 27, 1916

Nov 4, 1916 Electrocardiogram T inverted, then 1 5 mm positive in D I, inverted, then slightly positive in D II, inverted, then slightly positive in D III Normal P-R interval

Nov 10, 1916 Electrocardiogram T distinctly flattened in D I and D II, inverted in D III

Nov 25, 1916 Electrocardiogram T inverted 1 mm, then slightly positive in D I, inverted 2 55 mm in D II, inverted 1 55 mm in D III Normal P-R interval

Nov 29, 1916 Electrocardiogram resembles that of Nov 25, 1916

The pulse rate before giving digitalis showed a maximum of 120, minimum of 78, average for three days, 88 An intercurrent diarrhea,

November 6, with severe abdominal pain and temperature 99 4 for a few hours, was accompanied by pulse rate of 96 to 106, then the rate gradually dropped to 72, November 11, and a minimum of 68, November 19, but was always subject to rise on slight provocation

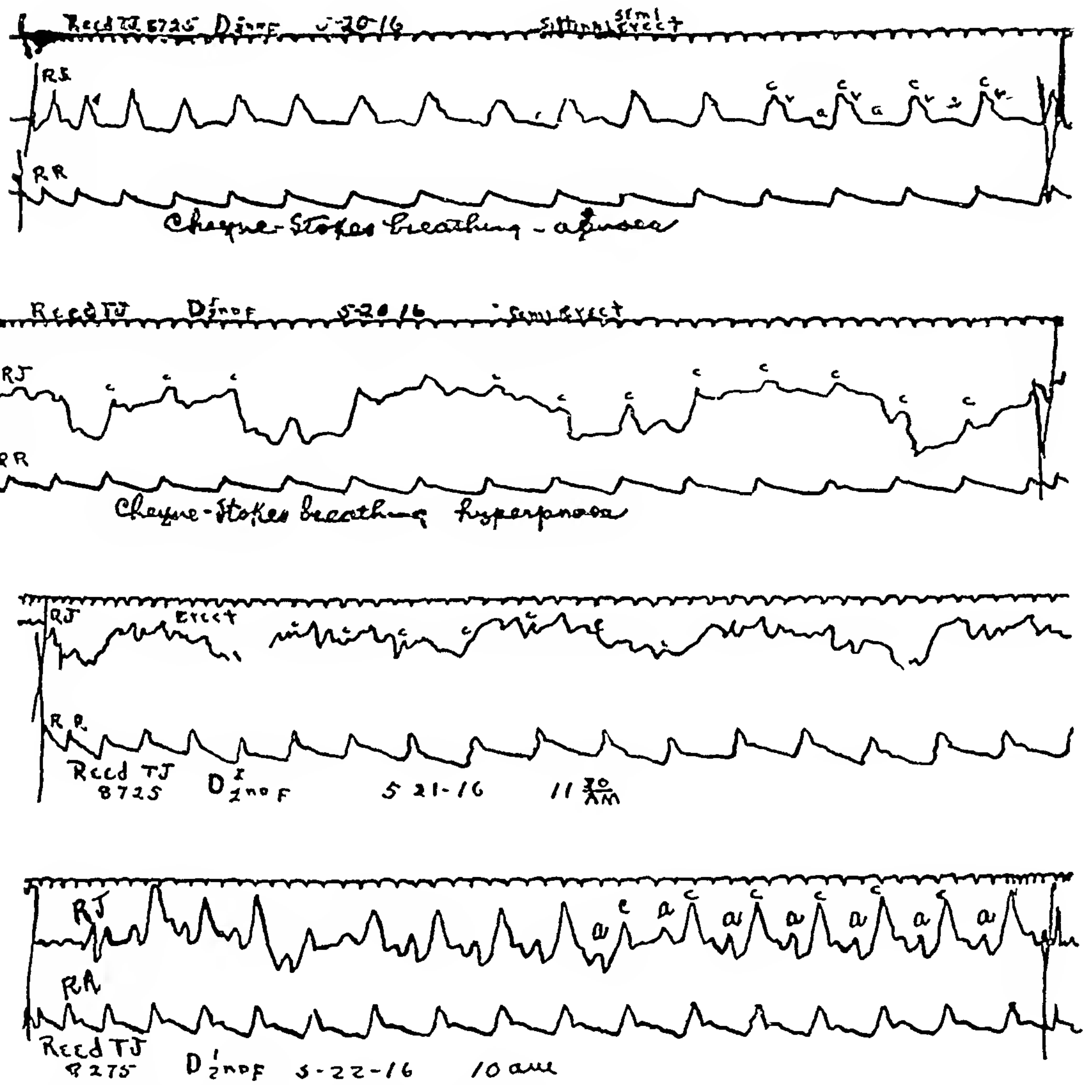

Fig 18—(Case 10) Polygrams May 20, 1916 (compare with Fig 17), show marked improvement in character of radial pulse (which is regular) within twenty-four hours after beginning digitalis May 21, 1916, shows greater improvement, and lowest tracing, May 22, 1916, shows auricular waves clearly

A distinct sinus arrhythmia was noted in this patient The only indication for digitalis was the rather high rate The physician referring the case suspected hyperthyroidism on this account, but this was not confirmed by the staff physician Marked improvement, probably due as much to rest as to drug, occurred

Case 9—J O (Hosp No 10026), was admitted Nov 16, 1916 Died Nov 30, 1917

Clinical diagnoses (1) carcinoma of stomach with metastatic carcinoma liver, (2) ascites, (3) pleural effusion, left, (4) dental caries

Weight 185 pounds The patient was given infusion *Digitalis lutea* as follows Nov 17, 1916, 90 c c and Nov 18, 1916, 90 c c (total 180 c c "Eggleston dosage") Nov 20 to Nov 22, inclusive, the patient was given tincture *Digitalis lutea*, 3 c c daily November 23 to November 28, inclusive, the patient was given tincture *Digitalis lutea*, 6 c c daily

Nov 17, 1916 Electrocardiogram T shows a small negative wave in all leads P-Q = 0 17 second Pulse rate, average 95

Nov 18, 1916 Electrocardiogram Slight increase in negativity of T-wave P-Q = 0 17 second Pulse rate averages 95

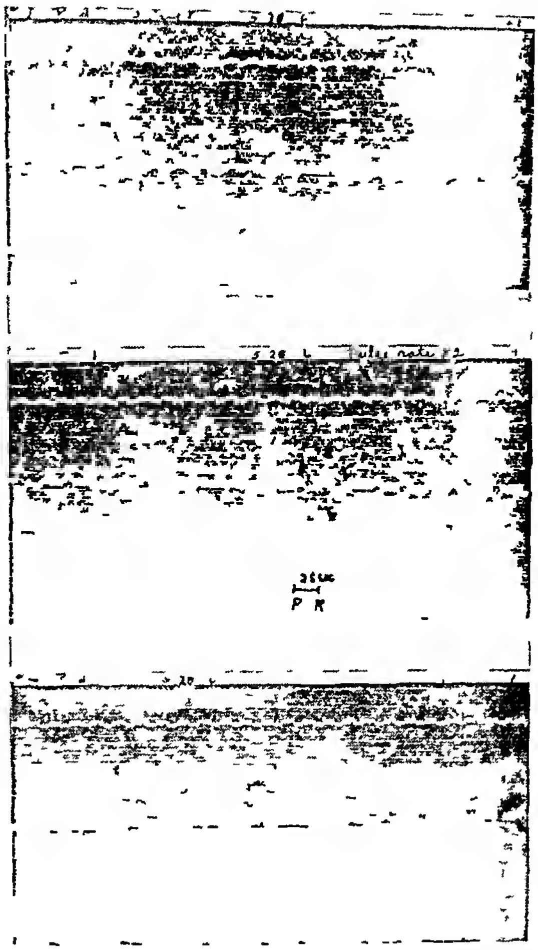

Fig 19—(Case 10) May 20, 1917 P-R = 0 25 second T-wave inverted in D I and D II, slight inversion in D III Pulse rate 82

Nov 20 and 21, 1916 Electrocardiogram T shows greater inversion in D I, November 20, also in D II, Nov 21, 1916 P-Q = 0 17 second Pulse rate averages 85

Nov 22, 1916 Electrocardiogram P-Q = 0 18 second More marked inversion of T-wave Pulse rate averages 72

In this case, again, it is possible that some digitalis had been taken before admission, although no history of this could be obtained An increase in negativity of T-wave is shown within eighteen hours after beginning the drug, and the pulse rate is slowed No essential change in the conduction time occurred though there is possibly slight slowing November 22, 1916

CASE 10—T J R, man (Hosp No 8725), was admitted May 18, 1916

Clinical diagnoses (1) syphilis, (2) chronic interstitial nephritis, (3) arteriosclerosis (general), (4) hypertension (238 systolic, 142 diastolic), (5) myocardial insufficiency

The blood showed urea nitrogen, 91, creatinin, 9 5, blood sugar, 0 21, phenolsulphonephthalein test, May 20, 1916, 27 per cent excreted in two hours

The patient received digitalis as follows May 19, 1916, infusion digitalis, 120 c c , May 20, 1916, infusion digitalis, 15 c c (total 135 c c = 4½ ounces,

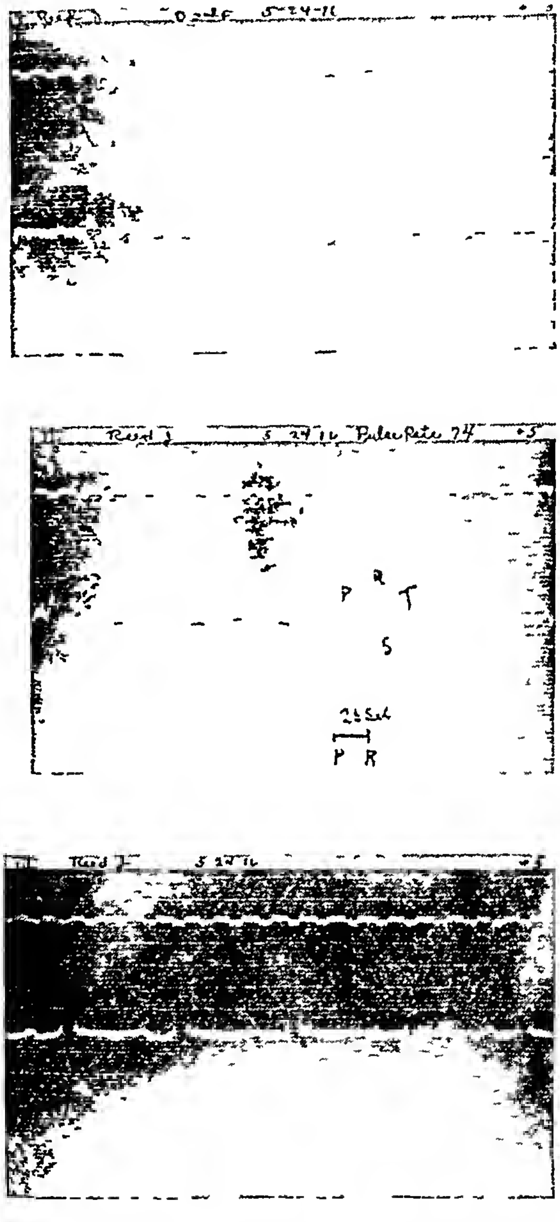

Fig 20—(Case 10) May 24, 1917 P-R = 0 25 second Inversion of T-wave increased in all derivations as compared with May 20, 1916 (Fig 19) Pulse rate 74

"Eggleston dosage"), then none until May 25 May 25 to June 5 the patient received tincture digitalis, minims 30 daily, then none until June 12, when tincture digitalis 2 c c (minims 30) daily were given until June 19 June 28, tincture digitalis 8 c c (minims 120)

May 19, 1916 Polygram (Fig 17) (before digitalis was given) shows small pulse, first strip taken during hyperpnea with Cheyne-Stokes breathing, second strip shows period of apnea

May 20, 21 and 22, 1916 Polygrams (Fig 18) show marked improvement in character of pulse wave Auricular waves have become clearly distinguishable in jugular pulse May 22, 1916

(No electrocardiographic tracing secured before digitalis was begun, but tracings shown later, July 11, 1916, show less inversion of T-wave than when showing digitalis effects, and P-R interval = 0 21 second)

May 20, 1916 Electrocardiogram (Fig 19) P-R interval = 0 25 second T inverted in D I and D II Slight inversion in D III Pulse rate 82

May 24, 1916 Electrocardiogram (Fig 20) P-R = 0 25 second T inverted in D I and D II and slightly inverted in D III Pulse rate 74

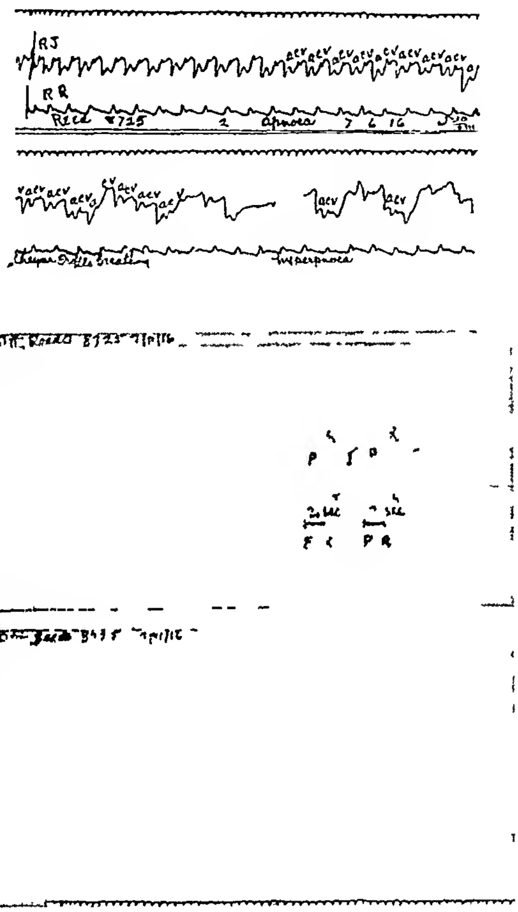

Fig 21—(Case 10) Electrocardiograms July 11, 1916 (no digitalis for thirteen days), P-R = 0 21 second T-wave inverted, then positive, in D I (not shown), inverted, then positive in D II and D III (has had no digitalis for thirteen days) (compare with Fig 19) Two short polygraphic strips

June 28, 1916 Electrocardiogram (No digitalis for eight days) T returning toward normal outline Pulse rate 65

July 11, 1916 Electrocardiogram (Fig 21) No digitalis for thirteen days P-R interval = 0 21 second T inverted, then positive in D I, inverted and then positive in D II T inverted, then positive in D III Polygraphic tracings taken show Cheyne-Stokes breathing in periods of apnea and hyperpnea, respectively

Died July 12, 1916 Necropsy refused

It is impossible to say in this case that no digitalis had been taken before admission It seems probable that there was some digitalis

effect, although no drugs had been taken for two weeks, since the P-R interval is prolonged to 0 25 second within eighteen hours after beginning the drug, and this interval is shorter at a later time, thirteen days after suspending We have not seen such a lengthening at such an early date in other instances, except where some digitalis effect was already present The lengthened P-R interval is the only evidence here of lessened conductivity in the bundle of His Partial block did not occur At one time, May 24, 1916, increased irritability of ventricular muscle is shown by extrasystole

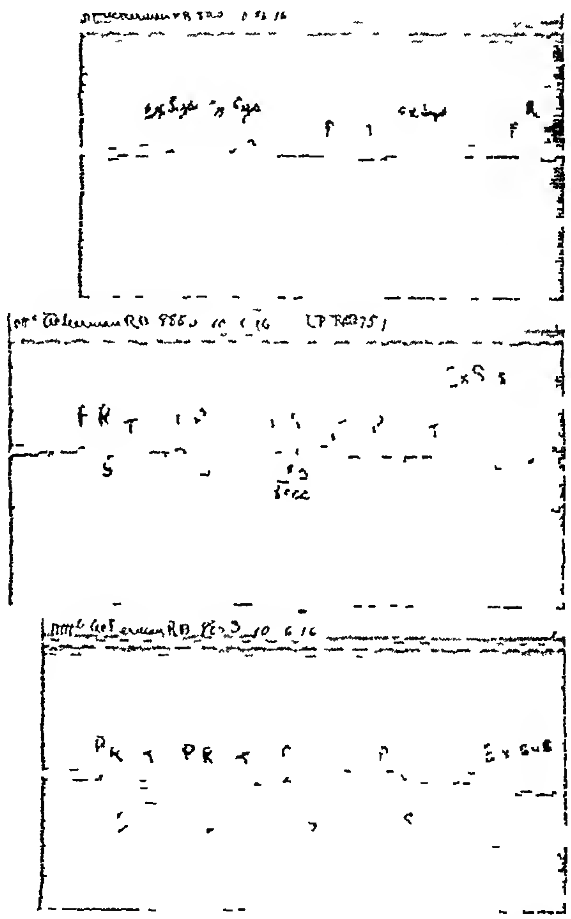

Fig 22—(Case 12) Oct 26, 1916 (before digitalis was given) P-R = 0 18 second T slight inversion in D I, iso-electric in early portion, then slightly positive in D II and D III Extrasystoles frequent Pulse rate 75

CASE 11—Mrs Sarah M, aged 30 (Hosp No 9870), was admitted Oct. 27, 1916, discharged Dec 21, 1916

Diagnoses (1) chronic valvular disease of heart with mitral insufficiency and stenosis, (2) hyperthyroidism (slight), (3) pyorrhea alveolaris and dental caries, (4) chronic amygdalitis

Weight, 111 pounds The patient was given infusion *Digitalis lutea* as follows

Nov 4, 1916, 54 c c, Nov 5, 1916, 54 c c (total 108 c c "Eggleston doses" in eighteen hours), Nov 7 to Nov 17, 1916, tincture digitalis 3 c c daily

Nov 4, 1916 Electrocardiogram P-R = 0 15 second T 3 mm positive in D I, 1 mm positive in D II, 2 5 mm negative in D III Pulse rate 80

Nov 9, 1916 Electrocardiogram Slight inversion of first portion of T-wave in D I and D II Inversion of T wave decreased in D III P-R interval = 0 17 second Pulse rate 92

Nov 17, 1916 Electrocardiogram P-R = 0 2 second T negative, then slight positive in D I Nearly iso-electric and diphasic in D II, iso-electric and slightly negative in D III Pulse rate 88

Nov 25, 1916 Electrocardiogram P-R interval much increased (0 31 second in D II) T shows slight inversion in D I, marked inversion in D II and D III Pulse rate 90

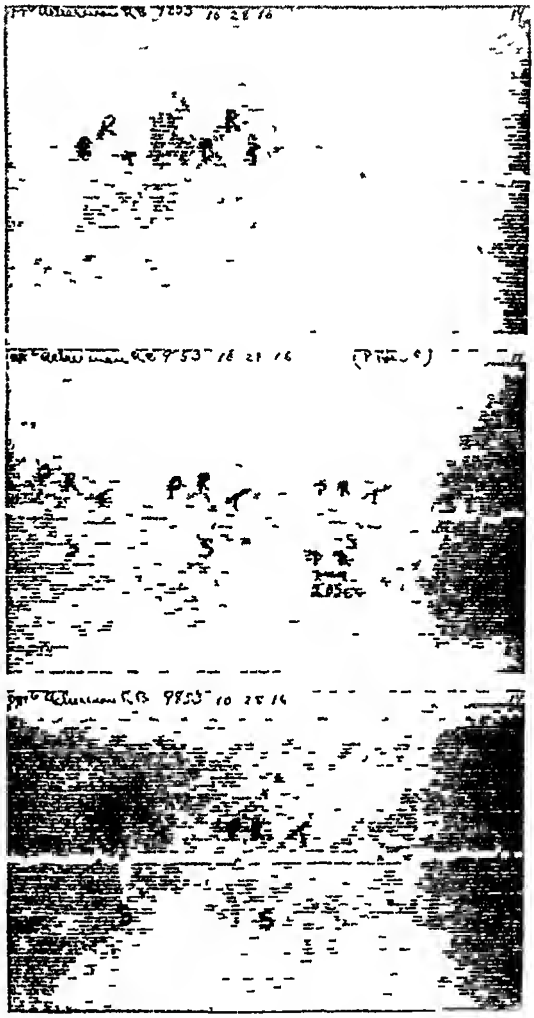

Fig 23—(Case 12) Nov 28, 1916, thirty-six hours after beginning Eggleston doses P-R = 0 2 second T-wave inverted in D I and D II, iso-electric, then slight inversion in D III Pulse rate 59

An occasional temperature rise to 99 4 F and once to 100 F gave rise to a suspicion of mild endocardial infection Repeated blood cultures showed no growth Average pulse rate was not decreased under digitalis, although the area of precordial dulness narrowed about 1 cm Irregularity of pulse from "missed beats" (?) was noted November 17, 1916 The patient was nauseated and vomited once November 18 while taking the official tincture (*purpurea*)

Digitalis caused not only a flattening, and later, inversion of T-waves, but also a gradual lengthening of P-R interval, this continuing to increase for at least seven days after suspension of the drug No blocking could be demonstrated then or later

Case 12—R B A, man, aged 59 (Hosp No 9853), was admitted Oct 25, 1916, discharged Nov 18, 1916

Clinical diagnoses (1) chronic diffuse nephritis, (2) arteriosclerosis with hypertension (185 systolic, 113 diastolic), (3) hypertrophy, dilatation and decompensation of heart, (4) anasarca, (5) pyorrhea alveolaris and dental caries

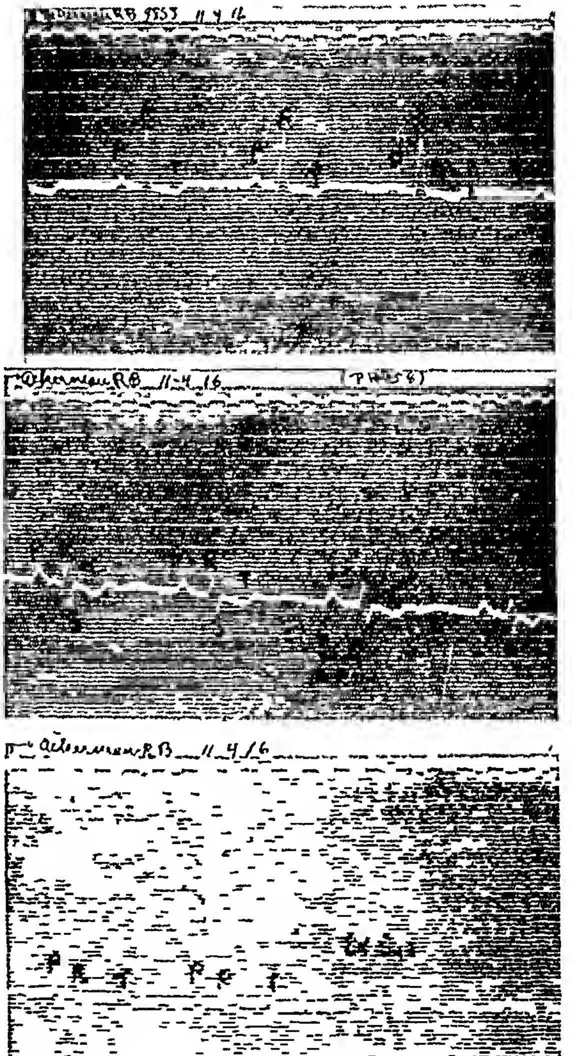

Fig 24—(Case 12) Nov 4, 1916 (nine days after last Eggleston dose, but after 3 c c of tincture on previous day) P-R = 0 24 second T-wave shows more inversion in D I and D II, nearly iso-electric and diphasic in D III Pulse rate 58

Weight 185 pounds The patient was given digitalis as follows

Infusion digitalis, 180 c c Oct 26 and Oct 27, 1916, in eighteen hours (Eggleston method), Nov 3 to Nov 18, 1916, tincture digitalis, 3 c c daily

Oct 26, 1916 Electrocardiogram (Fig 22) P-R = 0 18 second T wave slightly inverted in D I, iso-electric in early portion, then slightly positive in D II and D III Extrasystoles frequent Pulse rate 75

Oct 28, 1916 Electrocardiogram (Fig 23) P-R = 0 2 second T-wave inverted in D I and D II, iso-electric, then slight inversion in D III No extrasystoles Pulse rate 59

Nov 4, 1916 Electrocardiogram (Fig 24) P-R = 0 24 second T-wave shows more inversion in D I and D II, nearly iso-electric and diphasic in D III Pulse rate 58

Nov 17, 1916 Electrocardiogram (Fig 25) P-R = 0 22 second T-wave shows still more inversion in D I and D II, with small positive wave in D III Pulse rate 55

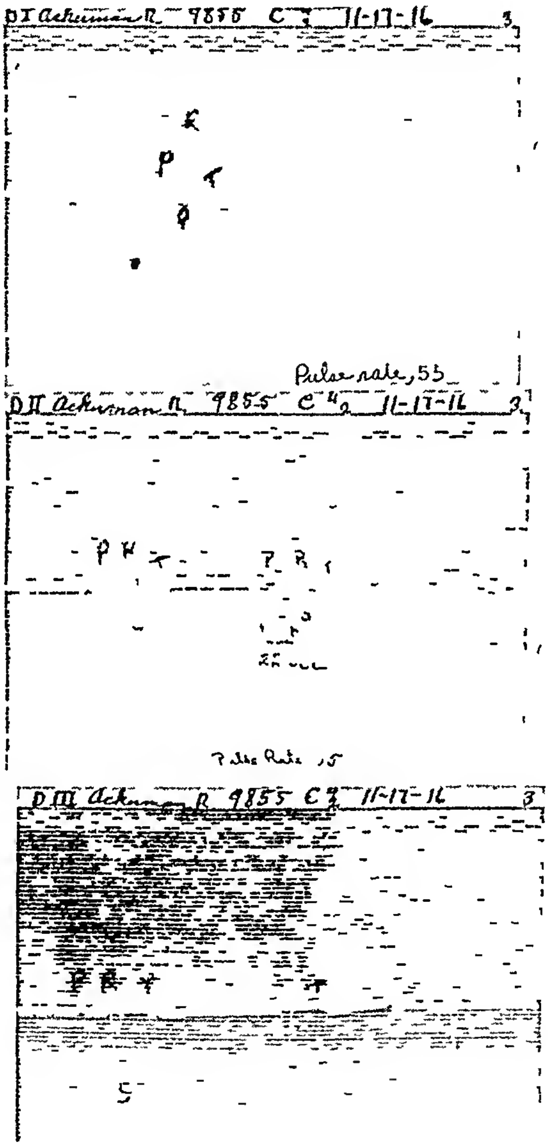

Fig 25—(Case 12) Nov 17, 1916 (after following Eggleston method with Tr digitalis, 3 c c daily for fourteen days) P-R = 0 22 second T-wave shows still more inversion in D I and D II with small positive wave in D III Pulse rate 55

A gradual lessening of rate from a normal rate of 75 to one of 55, three weeks later, occurred A gradual lengthening of P-R interval from 0 18 second before digitalis, to 0 24 second ten days after begin-

ning the drug, shows a definite depression of conductivity in the junctional tissues This is evident within thirty-six hours after beginning the Eggleston doses, but never reaches a high grade, and lessens somewhat even when 3 c c of tincture is being given daily (Compare Figs 24 and 25) Block did not occur Typical changes occur in the T-wave, evident also within thirty-six hours (Fig 23) and increasing during the administration of the small "tonic" doses The curves before beginning digitalis (Fig 22) suggest that the drug had been

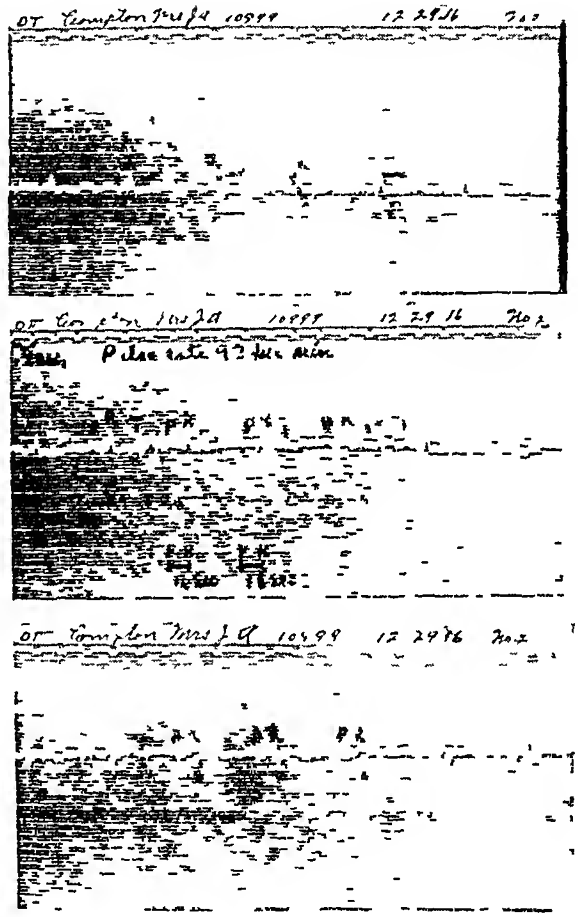

Fig 26—(Case 13) Dec 29, 1916 P-R = 0 16 second T is iso-electric or slightly inverted in all derivations Pulse rate 93

taken recently, and this suggestion is heightened by the presence of numerous extrasystoles The extrasystoles disappeared, however, when the drug was pushed, and other signs of digitalis action appeared

Throughout this study, this patient improved greatly, and the case illustrates the possibility of definite control with avoidance of undesirable effects when careful and frequent graphic studies are made

Case 13—Mrs J A C, aged 58 (Hosp No 10299), was admitted Dec 26, 1916, discharged Feb 6, 1917

Clinical diagnoses (1) pleurisy with effusion, left, (2) displacement of heart to right, (3) gingivitis

Weight 125 pounds The patient was given infusion *Digitalis lutea,* 120 c c in eighteen hours, Dec 31, 1916, and Jan 1, 1917, then tincture *Digitalis lutea,* 4 c c daily, Jan 3, 1917, to Jan 8, 1917

Dec 29, 1916 Electrocardiogram (Fig 26) P-R = 0 16 second T iso-electric or with possibly slight inversion in all derivations Pulse rate 93

Jan 6, 1917 Electrocardiogram (Fig 27) Partial block, T-wave distinctly inverted in D I and D II, no distinct change in D III Pulse rate 62

Jan 9, 1917 Electrocardiogram (Fig 28) Partial block continues, with T-waves showing no change from Jan 6, 1917 (Fig 27) Pulse rate 60 Immediately after taking this tracing the patient was given atropin sulphate 0 0017 gm (See Fig 29 taken twenty-four minutes later)

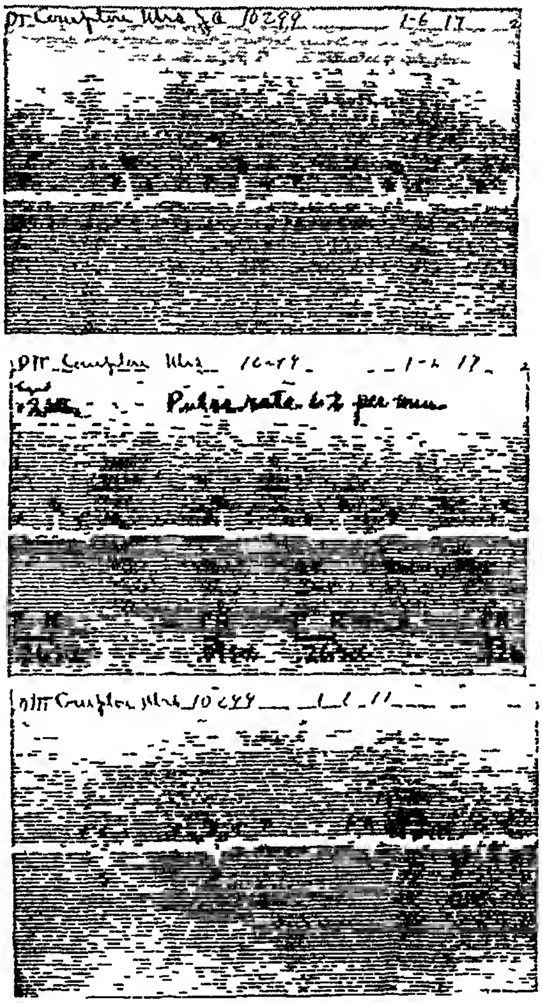

Fig 27—(Case 13) Jan 6, 1917, partial block T-wave distinctly inverted in D I and D II, no distinct change in D III Pulse rate 62

Jan 9, 1917, 9 47 to 9 49 a m Electrocardiogram (Fig 29) (taken twenty-four to twenty-six minutes after atropin sulphate 0 0017 gm hypodermically) P-R = 0 21 second Partial block has disappeared T-wave shows marked inversion in D I and D II, D III shows first portion of T-wave more strongly positive than in previous tracings Pulse rate 123

The clinical chart shows that this rapid, regular rate gradually disappeared and slow rate with partial block reappeared in six hours (Digitalis had been continued for two days after appearance of partial block (Jan 6, 1917) through an error, as the drug was ordered discontinued at once on recognizing the block)

Jan 11, 1917 Electrocardiogram, shows continuance of partial block, inversion of T-wave, and an occasional ventricular extrasystole, three days after last digitalis and two days after use of atropin

Jan 27, 1917 Electrocardiogram P-R = 0 14 to 0 17 second, somewhat irregular in length, but no block T-wave still shows some inversion in D I and D II D III cannot be distinguished from same derivation before taking digitalis

Jan 30, 1917 Electrocardiogram P-R = 0 16 second D I, D II and D III cannot be distinguished from same derivations before taking digitalis

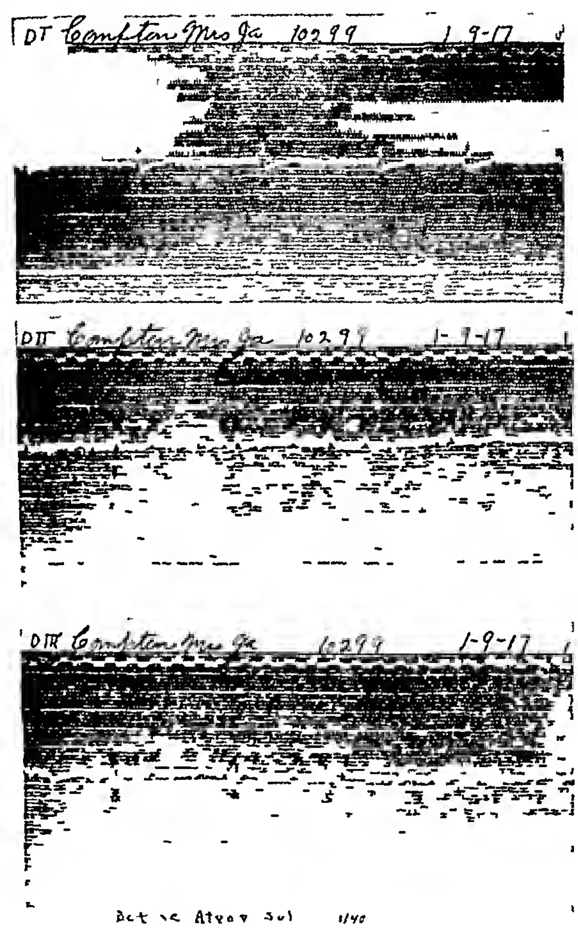

Fig 28—(Case 13) Jan 9, 1917, partial block continues T-waves as in Figure 27 Pulse rate 60

After taking the Eggleston doses there was no change in rate (104 to 116 per minute), but after beginning "tonic" doses the pulse gradually slowed to a minimum of 84, Jan 5, 1917 Jan 6, 1917 the pulse suddenly dropped to 60, with irregularity noted by the nurse (See also Fig 27) Atropin sulphate Jan 9, 1917 (Fig 29) removed the block, but caused no change in T-wave

There was no discomfort, and no untoward symptom and it was not thought necessary to continue atropin A digitalis effect on the T-wave is noted nineteen days after discontinuing the drug

Case 14—B H C, man, aged 53 (Hosp No 9860), was admitted Oct 26, 1916, discharged Dec 8, 1916

Clinical diagnoses (1) chronic myocarditis, (2) paralysis agitans, (3) pyorrhea alveolaris

Ophthalmoscopic examination showed some sclerosis of the retinal vessels Weight 161 pounds The patient was given infusion *Digitalis lutea* Nov 5, 1916, and Nov 6, 1916 (160 c c in eighteen hours, "Eggleston dose") Nov 7, 1916, to Nov 26, 1916, tincture digitalis 3 c c daily

Nov 4, 1916 Electrocardiogram (Fig 30) P-R = 0 18 second T 4 5 mm positive in D I, 4 mm positive in D II, slightly negative, then positive in D III Ventricular extrasystole in D III Pulse rate average 96

Nov 10, 1916 Electrocardiogram (Fig 31) P-Q = 0 21 second T negative, then 1 mm positive in D I, 3 mm negative, then slight positive in D II, 3 mm negative in D III Pulse rate, average 96

Nov 25, 1916 Electrocardiogram (Fig 32) Complete block Increased negativity of T-wave in all leads Pulse rate, average 55

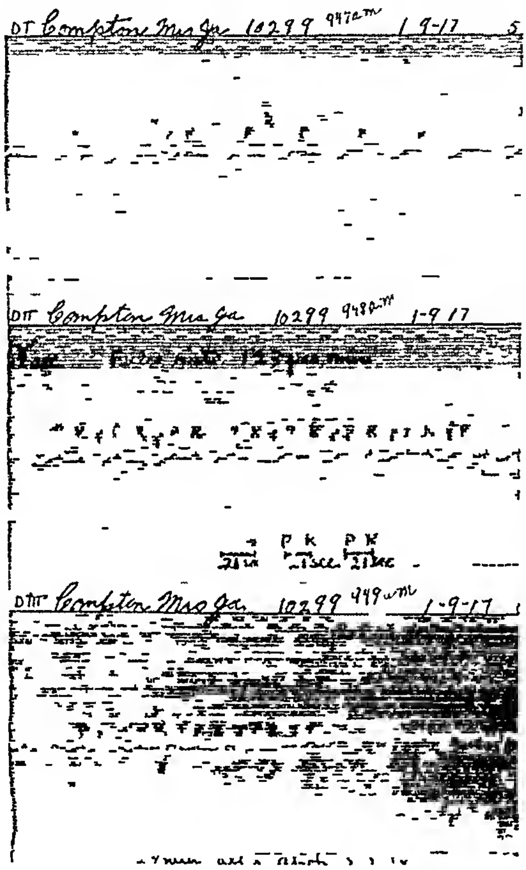

Fig 29—(Case 13) Jan 9, 1917 (twenty-four to twenty-six minutes after atropin sulphate 0 0017 gm hypodermically) P-R = 0 21 second Partial block has disappeared, T-wave marked inversion in D I and D II, first portion more strongly positive than in previous tracings in D III Pulse rate 123

Nov 26, 1916 Electrocardiogram Complete block continues Increasing negativity of T-wave Pulse rate, average 55

Nov 27, 1916 Electrocardiogram Complete block continues, as does negativity of T-wave All these phenomena lasted for ten days after suspension of digitalis, then disappeared gradually

Beginning with a normal (0 18 second) P-R interval, gradual lengthening of this interval occurred, with finally complete auriculo-ventricular dissociation, as shown in Figure 32, in which in D II the

ventricular rate is slightly lower than half the auricular rate, the alternate P-wave gradually merging in front of the R-wave In D III the ventricular rate is slightly faster than half the auricular, the alternate P gradually merging into R Inversion of the T-wave after digitalis occurs as in other cases

This is the only case of complete block from digitalis in our records It is of peculiar interest from the fact that the normal P-R interval

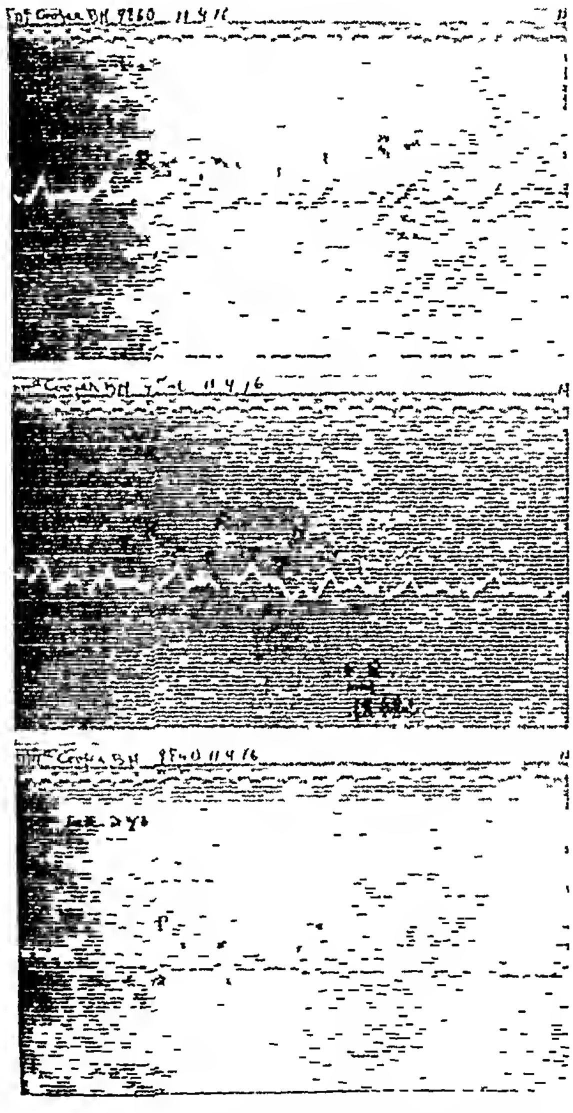

Fig 30—(Case 14) Nov 4, 1916 (before digitalis) P-R = 0 18 second T-wave positive, and high, in D I and D II, slightly negative and then positive in D III Pulse rate averages 96

before giving digitalis gave no hint of impaired conduction through the bundle

At the time of admission of this patient, and before giving *Digitalis lutea,* an occasional extrasystole was noted There was no increase in the frequency of extrasystoles, even though the block developed, with its consequent slower rate and greater opportunity for the occurrence of ventricular extrasystoles

Case 15—E U, man, aged 19 (Hosp No 7766)

Clinical diagnoses (1) chronic valvular disease of heart, mitral and aortic insufficiency and decompensation, (2) chronic passive congestion of liver, (3) ascites, (4) edema legs, (5) dental caries

Weight 170 pounds The patient was given tincture digitalis 3 c c daily from March 14, 1916, to March 31, 1916, then none until April 19, 1916, when 165 c c infusion digitalis, "Eggleston method," were given in eighteen hours.

March 8, 1916 Electrocardiogram P-R = 0 2 second T is a normal upward wave in D I, D II and D III

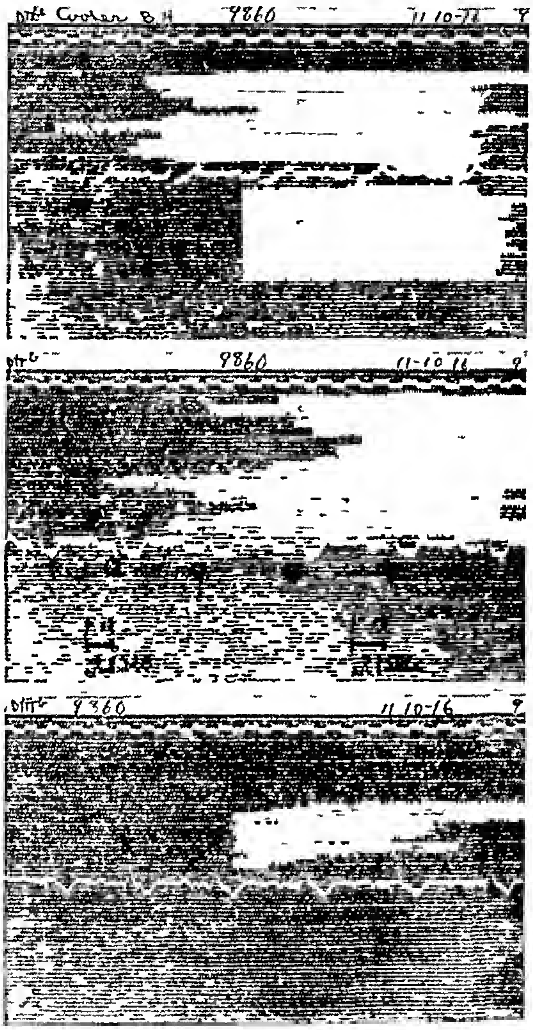

Fig 31—(Case 14) Nov 10, 1916 (Eggleston dose five days before and 3 c c tincture digitalis for three days just preceding this date) P-R = 0 21 second T shows marked inversion in all three leads, especially D II Pulse rate average 96

April 12, 1916 Electrocardiogram (has had 3 c c daily tincture digitalis for eighteen days, suspended twelve days before tracing taken) P-R = 0 22 second, except where an extrasystole has preceded, when it is 0 01 to 0 02 second longer T-waves of normal ventricular complexes like those of March 8, 1916, except for moderate flattening in D I Extrasystoles have been occurring before administration of digitalis

April 19, 1916 Electrocardiogram (no digitalis for nineteen days) Taken during attack of acute tonsillitis with temperature 104 F, with a very rapid and regular rate of 146 per minute, P-R = 0 25 second P superposed on T

April 20, 1916 Electrocardiogram (twenty hours after beginning Eggleston dosage) P-R = 0 24 T-wave shows distinct flattening in D II and D III as compared with April 12, 1916

April 26, 1916—Electrocardiogram Partial block (This has been occurring for three days, having begun three days after the Eggleston doses) T is a

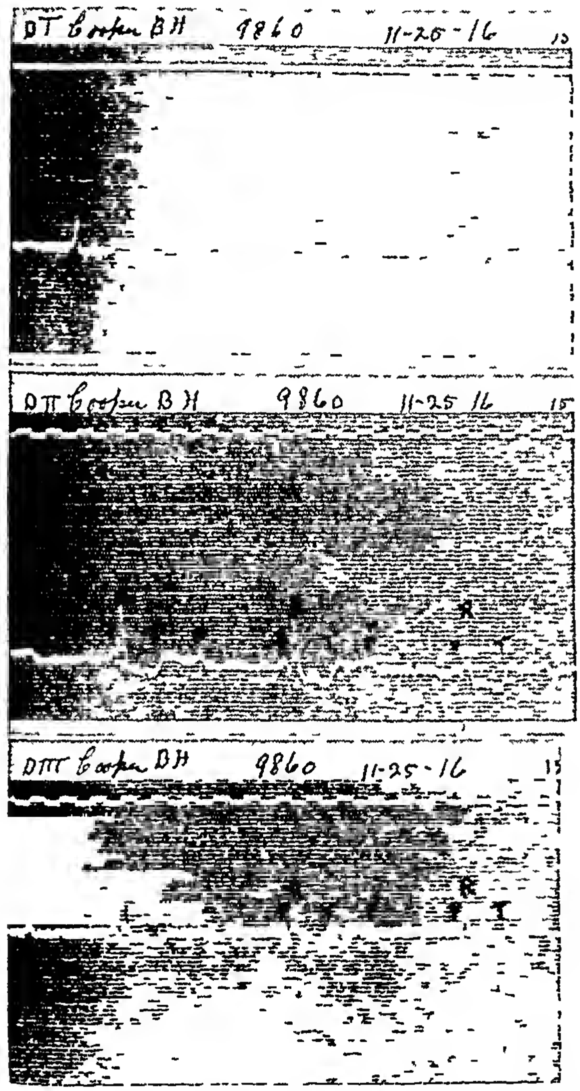

Fig 32—(Case 14) Nov 25, 1916 Complete block Increasing negativity of T-wave in all leads Pulse rate average 55

higher wave, more like that of March 8, 1916, than of April 20, 1916, after Eggleston doses

April 28, 1916 Electrocardiogram Partial block has disappeared P-R = 0 25 second There is a marked return of the form of T-waves toward that seen before digitalis Pulse rate 90 Ventricular extrasystoles occur

In this case, after having taken "tonic" doses of digitalis, an acute infection occurred with rapid pulse rate Digitalis in Eggleston doses, given at this time, caused, three days later, a partial block which lasted four days

The characteristic changes in T-waves occurred, and are shown at least twenty hours after beginning the drug The occurrence of extra-systoles was not due to the drug, but was distinctly lessened while the heart was definitely under its influence

SUMMARY AND CONCLUSIONS

Our impression is that the Eggleston method is a valuable addition in digitalis therapy, that it gives confidence in the use of the drug, and that the shorter time necessary for securing digitalis effects should give the method wide use

The method must be used with care to select cases in which these effects are desired Cases of acute or chronic infections, with the probability of the presence of endocardial infections, should be given the method—if at all—only after careful study, because of the possibility of embolism and, quite as important, in our opinion, the possibility of associated myocardial changes predisposing to block

The method requires careful study of the patient before, during, and after its administration, and, since it produces powerful and clear-cut effect, should be used with extreme care and judgment

The graphic methods of study show that when given in large enough doses, as by the Eggleston method, digitalis effects may be secured in from sixteen to twenty-four hours

The electrocardiogram provides a means of accurate study of these effects, showing alterations in the T-wave in all cases studied and also alterations—principally an increase—in conduction time in many

Alterations in outline of the T-wave accompany physiologic effects of digitalis, and such alterations may persist for many days after withdrawing the drug In Case 13, persistence of altered T wave is shown for 19 days, in Case 2, 20 days In Cases 7, 11, 10 and 2 alteration was found for 6, 8, 13, and 14 days, respectively In our other studies of digitalis action we find it not uncommon for such alterations to persist for 10 days to 2 weeks, the T-wave gradually returning to its normal outline

The Eggleston method, in cases of decompensation with auricular fibrillation, gives strikingly favorable results Digitalis effects are shown in from twelve to twenty-four hours in four of our cases (Cases 1, 2, 4 and 5) This is much earlier than results obtained by administering digitalis by older methods, and may therefore be responsible for saving life and is of great clinical significance In one case (Case 3) electrocardiographic records were not secured until thirty-six hours had elapsed, but a marked effect is shown at this time, and in this case a tremendous urinary output began within twenty-four hours

We have not seen the Eggleston doses result either in extrasystoles or in heart block, except in cases giving presumptive evidence of previous digitalis administration (Case 3 showed paired beats, Case 10, extrasystoles irregularly placed, and Case 15 showed partial heart block of short duration) In one case (Case 12) prolongation of conduction time from 0 18 to 0 24 second occurred

The Eggleston method, with 3 or 4 c c or more of the tincture daily for several days, has resulted, once in partial and once in complete heart block (Cases 13 and 14) In several instances there has been lengthening of the P-R interval without this becoming so great as to cause block In these instances no unfavorable effects were noted, and careful watching, with study by graphic methods, has allowed control with prevention of the more severe manifestations of toxic action

The number of cases in our series is too small to be conclusive as to the time of occurrence of the various effects of digitalis, but in general it appears that in addition to the moderate degree of slowing of the pulse rate, due to a vagus effect on the sino-auricular node, three distinct effects of digitalis may be noted

(*a*) Inversion of the T-wave, due probably to some effect on conduction through either the finer ramifications of the system of Purkinje fibers, or the musculature itself, or both This effect is constant in occurrence and accompanies both the desirable and undesirable effects of digitalis, increasing in degree with increase in the amount of the drug given and persisting for several days, often as much as two weeks, and occasionally nearly three weeks, after withdrawal of the drug This effect is the first to appear and the last to disappear

(*b*) Delay in conduction through the bundle of His The desirability of this effect varies with the conditions in the heart In auricular fibrillation it is probably largely responsible for the brilliant results so often secured in decompensation with rapid, irregular heart action In this condition digitalis should be given boldly and with confidence, and the Eggleston method gives most satisfactory results

In individuals without auricular fibrillation but with a presumably normal conducting tissue, digitalis may be given by the Eggleston method apparently without harm, but no such striking improvement is seen as in cases with auricular fibrillation

In those patients giving evidence of impaired conduction, as shown by a P-R interval of 0 2 second or over, digitalis must be given with great caution, if at all, and then only in the presence of clear indications for the use of the drug Any evidence of partial block contraindicates its use or further administration

The effect on the conducting tissues appears later and after larger

doses than the effect on the T-wave, except possibly in cases where some impairment of the conducting tissues already exists It is probable that auricular fibrillation causes some impairment of conduction, or at least renders the conducting tissues sensitive to digitalis, the great frequency of conducted impulses causing a certain degree of exhaustion of the tissue This impairment may explain in part the prompt, favorable effects of the drug in this condition

(*c*) Extrasystoles, ventricular in origin, due to increased irritability of the heart muscle This effect is undesirable under any circumstances and appears usually last of the three noted, except where the conducting tissues are presumably healthy and not overworked, in which case extrasystoles as a result of digitalis action may occur before changes in conduction time are seen

Digitalis lutea, the Minnesota first-year leaf, produces effects apparently identical with those of the official *Digitalis purpurea,* except, possibly, so far as nausea and vomiting are concerned We have seen these phenomena in man only once after the use of very heavy doses of *lutea* and are encouraged in studying this drug further with the hope of finding a preparation with digitalis action that produces less of these annoying effects

We suggest the further trial of *Digitalis lutea,* and recommend that it be standardized on the basis of "cat unit" rather than on the basis of content of digitalis leaves In this way a preparation would be available with known physiologic effect, and dosage could be calculated on the basis of body weight

ANTIGEN-ANTIBODY BALANCE IN LOBAR PNEUMONIA *

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While it is recognized that the course and outcome in any individual case of lobar pneumonia is probably determined by the ability of the body to overcome the disease by the elaboration of substances antagonistic to the progress of the infection, it is not definitely known what the relative importance of the various immunity principles involved is, nor what factors serve to tip the balance favorably or otherwise in the struggle between antigen and antibody

It has been known for some time that natural recovery from pneumonia is attended by the development of certain humoral antibodies which appear shortly before or at the time of crisis In 1891 G and F Klemperer[1] showed that the blood of patients who had recovered from the disease might protect rabbits against infection with the pneumococcus This fact was confirmed by Neufeld and Handel,[2] who also showed that similar protection might be afforded to mice Dochez[3] showed that the appearance of these protective substances coincided rather sharply with the period of critical fall in temperature in many instances Besancon and Griffon,[4] Chickering[5] and others have shown that agglutinins appear in the blood of patients ill of and convalescent from lobar pneumonia and Clough[6] has noted that, in certain instances, serum from convalescent cases possesses the power of inducing in vitro phagocytosis of virulent pneumococci which are not phagocytable in normal serum That these humoral antibodies are effective only against the homologous type of pneumococcus is now well recognized Whether the development of humoral antibodies in itself is primarily responsible for recovery, or is merely an expression of the development of a cellular defensive mechanism, is not known It seems highly probable, however, from the studies of Cole[7] and of Bull[8] that humoral immunity is an exceedingly important factor in bringing about recovery from the disease

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* From the Department of Medicine, University of Minnesota, Minneapolis

1 Klemperer, G and F Berl klin Wchnschr, 1891, **28,** 833, 869
2 Neufeld, F, and Handel Arb a d k Gsndhtsamte, 1910, **34,** 166
3 Dochez, A R Jour Exper Med, 1912, **16,** 665
4 Besancon, F, and Griffon, V Compt rend Soc de biol, 1897, **6,** 551, 579
5 Chickering, H T Jour Exper Med, 1914, **20,** 599
6 Clough, P W Bull Johns Hopkins Hosp, 1913, **24,** 295
7 Cole, R Jour Exper Med, 1917, **26,** 453
8 Bull, C G Jour Exper Med, 1915, **22,** 457

It is well established that pneumococcus antigen in the form of living pneumococci is present in the blood in a considerable proportion of cases of pneumonia, and in general it may be said that pneumococci tend to disappear rapidly from the blood in cases that progress to recovery, but that they increase and a true pneumococcemia develops in cases that terminate fatally, provided there are no serious complications that influence the outcome Furthermore, Dochez and Avery[9] have shown that a soluble pneumococcus substance which can be detected by means of the precipitin reaction is produced in the body during the course of the disease, that it is present in demonstrable amounts in the blood in a small number of cases unusually severe, and that it is excreted in the urine in a considerable percentage of cases at some time during the course of the disease and often during convalescence They have found that the amount of this substance present in the urine varies in different individuals and that the presence of a large amount is of unfavorable prognostic import Cole[7] has also shown that a large amount of soluble substance, presumably of pneumococcus origin, is present in empyema fluids and in the blood of infected rabbits, which possesses the power of neutralizing pneumococcus antibodies He considers that the rapid disappearance of pneumococcus antibodies from the blood of severely infected patients who have been treated with antipneumococcus serum is probably associated with the presence of such soluble substances in the blood The nature of this substance is not definitely established, but it seems probable that it is the same substance which gives rise to precipitins in the blood and urine of infected patients demonstrated by Dochez and Avery [9]

With these conceptions as a basis, the following study was undertaken with the purpose of determining the antigen-antibody balance, if we may speak of it as such, in a series of cases of lobar pneumonia, in order to determine (1) the relation of antigen to antibody, (2) what relation the antigen-antibody balance bears to the course, clinical severity, and final outcome of the individual case, and (3) whether such studies might be of prognostic value in the individual case The cases studied have been on the wards of the Elliot Memorial Hospital, University of Minnesota, and the Minneapolis City Hospital No special line of treatment has been followed and no specific serum therapy has been used In all, nineteen cases have been completely studied and form the basis of this report All cases have been classified with respect to the type of pneumococcus causing the infection [10]

Twelve were due to infection with Type I pneumococcus, all of which recovered, 4 with Type II pneumococcus, 3 of which recovered,

9 Dochez, A R, and Avery, O T Jour Exper Med, 1917, **26,** 477
10 Dochez, A R, and Gillespie, L J Jour Am Med Assn, 1913, **61,** 727

1 died, 2 with Group IV pneumococcus, of which 1 recovered, 1 died, and 1 was caused by Friedlander's bacillus with fatal termination While it is realized that the number of cases studied is small, it has seemed advisable to report the results so far obtained, the further progress of the work having been interrupted at present by the war

The general plan of study has consisted of daily blood cultures throughout the course of the disease, daily determination of the concentration of soluble pneumococcus substance, of agglutinins and of precipitins in the blood serum throughout the course of the disease and at intervals during convalescence, and daily determinations of the concentration of soluble pneumococcus substance excreted in the urine throughout the period of observation In determining the concentration of soluble pneumococcus substance and of antibodies the dilution method, in dilutions of 1 1, 1 2, 1 4, 1 8, etc, with 0 85 per cent salt solution as a diluent, has been used The highest dilution in which a positive reaction occurred has been taken as a measure of the concentration of the substance sought The term "soluble antigen" will be used hereafter to designate the soluble substance of pneumococcus origin found in the blood and excreted in the urine

METHODS

The methods were as follows

Blood Cultures—Blood was collected by venipuncture by the usual technic Eight to 10 c c were inoculated into a flask of plain broth and measured amounts from 1 c c to 5 c c were poured in agar plates to determine the number of pneumococci per cubic centimeter of blood

Soluble Antigen in the Blood—Detected by the precipitin method Five-tenths c c of a 1 10 dilution of the homologous type of antipneumococcus serum[11] was added to 0 5 c c of increasing dilutions of the patient's serum in a series of small tubes and incubated for two hours at 37 C Final readings were made after the tubes had stood in the ice box over night

Soluble Antigen in the Urine—Detected by the precipitin method A sample of urine, collected shortly before the daily bleeding, was rendered clear by filtration, 0 5 c c of a 1 10 dilution of the homologous type of antipneumococcus serum was added to 0 5 c c of increasing dilutions of the urine in a series of small tubes and incubated for one hour at 37 C, when final readings were made In calculating the amount of soluble antigen in the urine, the final calculation was made on the basis of a constant daily excretion of 1,000 c c of urine, inasmuch as the concentration rather than the actual amount of soluble antigen was being measured

Serum Agglutinins—To 0 9 c c of increasing dilutions of the patient's serum, 0 1 c c of an eighteen-hour broth culture of the homologous type of pneumococcus was added The tubes were incubated for two hours at 37 C and final readings were made after the tubes had stood in the ice box over night

Serum Precipitins—To 0 5 c c of increasing dilutions of the patient's serum in a series of small tubes, 0 5 c c of a standard soluble pneumococcus antigen was added The tubes were incubated for two hours at 37 C, the final readings being made after the tubes had stood in the ice box over night

11 The antipneumococcus serum employed was that prepared at the Hospital of the Rockefeller Institute for Medical Research, New York

EXPERIMENTAL

The cases studied have fallen into three groups with respect to the results obtained (1) clinically mild cases with recovery in which blood cultures have been negative and in which no soluble antigen was demonstrable in the blood serum or urine during the course of the disease, (2) clinically severe cases going on to recovery with positive blood cultures early in the course of the disease and excretion of considerable amounts of soluble antigen in the urine, but without demonstrable soluble antigen in the blood serum, (3) fatal cases with positive blood cultures and increasing amounts of soluble antigen in both blood and urine until time of death These groups will be presented separately with typical examples from each group

Group 1—The first group consists of eleven cases, of which nine were due to infection with Type I pneumococcus, one with Type II pneumococcus, and one with Group IV pneumococcus [12] All the cases with the exception of the Type II case were clinically mild and all recovered Two examples are given

CASE A 16—E M H No 12533 Type I pneumococcus Entered the hospital on the third day of the disease in good condition Course uneventful, with recovery by crisis on the sixth day Blood cultures negative No soluble antigen present in the blood nor excreted in the urine throughout the period of observation Agglutinins for Type I pneumococcus appeared in the blood on the fifth day twenty-four hours before crisis in a dilution of 1 12, rising to 1 4 on the sixth and seventh days, 1 8 on the eighth day and 1 16 on the twelfth day Precipitins for Type I pneumococcus antigen appeared in the blood on the seventh day twenty-four hours after crisis in a dilution of 1 1, rose to 1 8 on the eighth day and fell off to 1 4 on the twelfth day (Chart 1)

CASE A 30—M C H No D 5451 Type I pneumococcus Entered the hospital on the third day of the disease Clinical condition good Course uneventful Recovery by lysis from the seventh to the twelfth days Empyema developed on the eighteenth day Thoracentesis Sterile pus withdrawn Recovery without operation Blood cultures negative No soluble antigen present in the blood or excreted in the urine during the course of the disease On the twenty-seventh day small amounts of soluble antigen appeared in the urine for the first time and was excreted the next two days when observation of the case ended Agglutinins appeared in the blood in a dilution of 1 4 on the seventh day when lysis began, rose to 1 16 on the eighth day, 1 32 on the tenth day and maintained that level during the remainder of the period of observation Precipitins appeared in the blood on the seventh day in a dilution of 1 1 simultaneously with beginning lysis, rose to 1 8 on the eighth day, 1 32 on the tenth and thirteenth days, fell off to 1 16 on the seventeenth day and to 1 4 on the twenty-eighth day at the time when soluble antigen appeared in the urine (Chart 2)

Of the eleven cases in this group nine showed negative blood cultures throughout, two showed positive blood cultures on one day only, in both instances less than one colony per 3 c c of blood None of the cases at any time showed soluble pneumococcus antigen in the blood

12 Soluble antigen was not determined in this case as no immune serum was available

and none of the patients excreted soluble antigen in the urine in demonstrable amounts during the course of the disease Six patients excreted small amounts at some time during convalescence, usually from one to two weeks after crisis Five patients did not excrete soluble antigen in the urine up to the time when observation ended

Agglutinins for the homologous pneumococcus appeared in the blood in all cases, in seven, from twenty-four to forty-eight hours before crisis or beginning lysis, in one, coincident with beginning lysis, and in two very mild cases with crisis, on the fourth and fifth days, respectively, not until twenty-four hours after crisis The concentra-

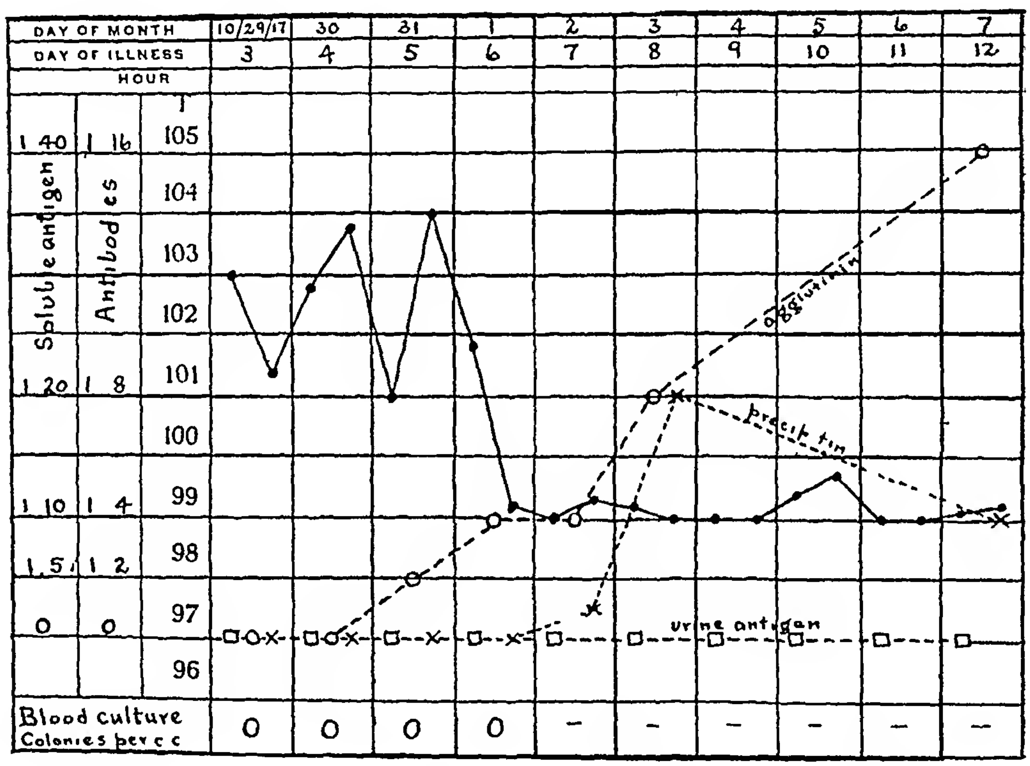

Chart 1—Case A 16 Lobar pneumonia Type I pneumococcus

tion of agglutinins increased rapidly at the time of recovery and remained elevated during convalescence Precipitins appeared in the blood in all cases in one, twenty-four hours before the appearance of agglutinins, in four at the same time, and in six, from twenty-four to forty-eight hours later The precipitin concentration usually rose shortly after crisis, but showed a marked tendency to fall rather rapidly to a low level simultaneouly with the appearance of soluble antigen in the urine, as shown in Case A 30 (Chart 2)

Group 2—The second group includes five cases Three were due to infection with Type I pneumococcus, two with Type II pneumococcus All were clinically severe but the patients recovered One example is given

Case A 29—M C H No D 5326 Type I pneumococcus Entered the hospital on the third day of the disease Clinical condition serious Recovery by lysis from the sixth to eighth days Convalescence uneventful Blood culture showed 102 colonies of Type I pneumococcus per cubic centimeter of blood on the fourth day Two colonies per cubic centimeter on the fifth day, negative on the sixth and seventh days Soluble antigen was excreted in the urine in considerable amounts It was detectable in a dilution of 1 8 on the fourth day, rose to 1 20 on the fifth day, fell off to 1 6 on the sixth day coincident with beginning lysis, and continued to be excreted in moderate amounts during the remainder of the period of observation Soluble antigen was never present in detectable amounts in the blood Agglutinins appeared in the blood on the sixth day in a dilution of 1 1 coincident with beginning lysis, rose to 1 4 on the seventh day, 1 16 on the eighth day and fell off to 1 8 on the twelfth day Precipitins did not appear in the blood at any time (Chart 3)

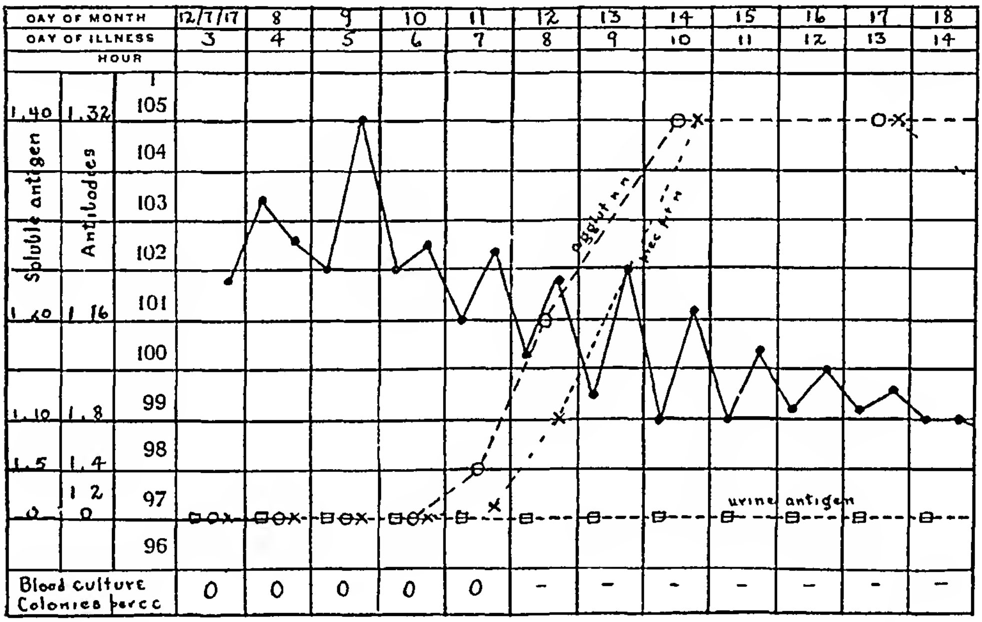

Chart 2A—Case A 30 Lobar pneumonia Type I pneumococcus

Of the five cases in this group three showed positive blood cultures early in the disease, which became negative as the disease progressed Two patients entering the hospital on the fourth and seventh days of the disease, respectively, showed negative cultures at that time None of the cases showed soluble pneumococcus antigen in the blood at any time All excreted considerable amounts of soluble antigen in the urine throughout the course of the disease, with a decrease in the amount shortly before or coincident with recovery All continued to excrete moderate amounts throughout convalescence, usually with a secondary rise in concentration about a week after crisis

Agglutinins appeared in the blood before or at the time of crisis in all cases exactly as in cases of the first group, and rose in concentration after crisis, reaching a dilution of 1 8 in three instances, 1 16 in two

In contrast with cases of the first group, the concentration of agglutinins tended to diminish during convalescence Precipitins did not appear in the blood in any instance in the cases of this group even during convalescence, a feature in striking contrast with the results obtained in the first group

Group 3—The number of cases in this group is very limited, being only three in number, one case due to Type II pneumococcus first seen on the sixth day, the patient dying on the seventh, one case due to Group IV pneumococcus in which no data on the presence of soluble antigen in the blood or urine are available, and one case caused by Friedlander's bacillus, in which the data are complete This case is

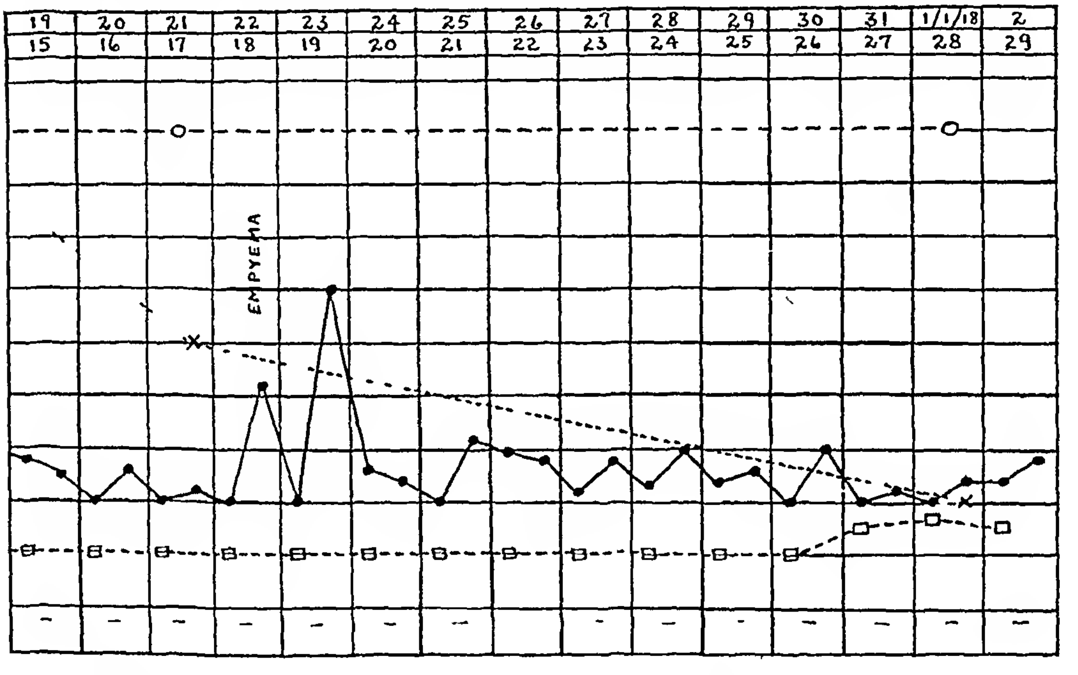

Chart 2B—Case A 30 Lobar pneumonia Type I pneumococcus

presented as representative of the group because it shows the probable course of events in most fatal cases of pneumococcus pneumonia, and because, so far as is known, it is the first case of Friedlander's bacillus pneumonia in which studies of this nature have been made The immune serum for determining the presence of soluble antigen in the blood and urine was obtained by the immunization of a rabbit with the strain of Friedlander's bacillus isolated from the patient's blood

Case A 24—M C H No 5044 Friedlander's bacillus pneumonia The patient entered the hospital on the fifth day of the disease in fairly serious condition Progress was steadily downward and death occurred early in the morning of the ninth day Blood cultures were negative on the fifth and sixth days, showed two colonies of Friedlander's bacillus per cubic centimeter of blood on the seventh day, and seventeen colonies per cubic centimeter on the eighth day, eighteen hours before death Soluble antigen appeared in the blood

on the sixth day in a dilution of 1 1, rose to 1 2 on the seventh day and to 1 8 on the eighth day Soluble antigen was excreted in the urine in a dilution of 1 2 on the fifth and sixth days and rose on the seventh and eighth days, reaching a dilution of 1 8 No agglutinins or precipitins appeared in the blood (Chart 4)

The two other cases of this group showed positive blood cultures, the Type II case having 36 pneumococci per cubic centimeter of blood on the sixth day, 73 per cubic centimeter on the seventh day shortly before death, the Group IV case having a positive culture for the first time on the seventh day, sixteen hours before death, with 12 pneumococci per cubic centimeter of blood Neither case developed agglutinins or precipitins The Type II case showed soluble antigen in the blood in a dilution of 1 2 on the sixth day, 1 4 on the seventh day No urine determinations were made as the patient was incontinent

DISCUSSION

Certain interesting facts have developed from the study All patients who have consistently failed to excrete detectable amounts of soluble pneumococcus antigen in the urine during the course of the disease have recovered Whether this will prove a universal rule in all cases, provided there is no serious complicating factor, only the study of further cases can determine It is significant that in a group of eighty-eight cases in which the excretion of soluble antigen in the urine was studied by Dochez and Avery[9] only two patients who showed negative urine reactions died, one due to an atypical Group II pneumococcus, the other to a Type III pneumococcus It will be readily understood that this finding cannot apply to cases of pneumonia caused by Group IV pneumococci, inasmuch as no antipneumococcus serum is available for making the test in such cases If this rule is found to be generally applicable, its great value as a prognostic measure is evident

Patients who have failed to excrete soluble antigen in the urine during the course of the disease frequently begin to excrete it in small amounts at some period during convalescence Also, patients who excrete it during the course of the disease, if they recover, usually show a secondary rise in the amount excreted at a corresponding time This is apparently coincident with the period of resolution It is suggested that it is associated with the liberation of antigen from the resolving pneumonic consolidation

Agglutinins have invariably appeared in the blood of all patients who have recovered, usually twenty-four to forty-eight hours before crisis The concentration of agglutinins has risen rapidly at the time of recovery, remaining elevated during convalescence in the milder cases, showing a tendency to fall off in the severer cases On the

other hand, fatal cases have failed to develop demonstrable agglutinins No apparent relation between the excretion of urinary antigen and the development of agglutinins has existed

All patients who have developed precipitins in the blood have recovered, but not all that have recovered have developed demonstrable precipitins In fact, the appearance of precipitin and the curve of its concentration has seemed to bear no definite relation either to the agglutinin curve or to recovery The appearance of precipitin, however, has borne a very striking relation to the excretion of soluble antigen in the urine, in that all patients who have failed to excrete

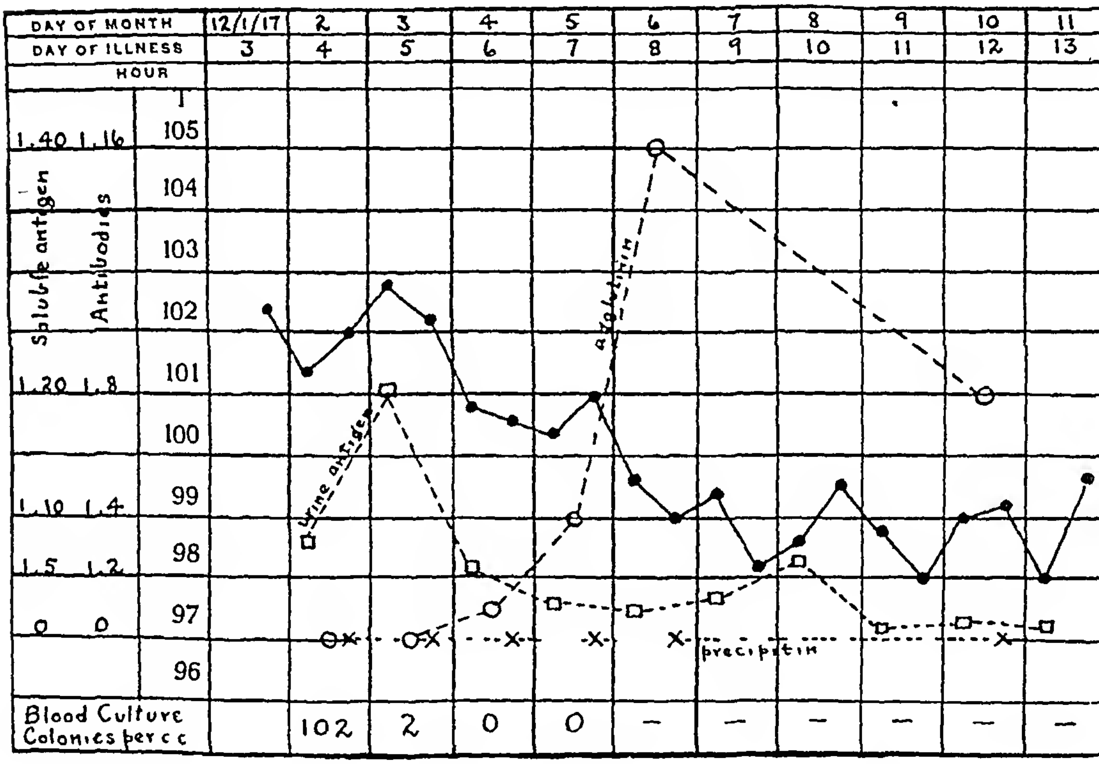

Chart 3—Case A 29 Lobar pneumonia Type I pneumococcus

soluble antigen in the urine during the course of the disease have developed precipitins in the blood at or about the time of crisis, while all patients excreting soluble antigen during the course of the disease have failed to develop precipitin in the blood Furthermore, in those cases developing precipitins the concentration, after rising rapidly during the period shortly after crisis, has fallen rather abruptly coincident with the appearance of soluble antigen in the urine

In consideration of these phenomena it is well to bear in mind that in measuring the concentration of precipitin we are probably dealing only with the excess, or free precipitin above that which is bound or neutralized by the soluble antigen If this be so, it seems plausible to explain the course of events as follows In those patients who fail to

excrete soluble antigen during the course of the disease, it is probable that the development of precipitin in the body keeps pace with the elaboration of the antigen and that the two serve to counterbalance or neutralize each other until finally at or about the time of crisis the development of precipitin exceeds the formation of soluble antigen, and free precipitin appears for the first time in the blood The subsequent decline in the concentration of precipitin during convalescence coincident with the appearance of soluble antigen in the urine would seem to be associated with the liberation of a considerable amount of

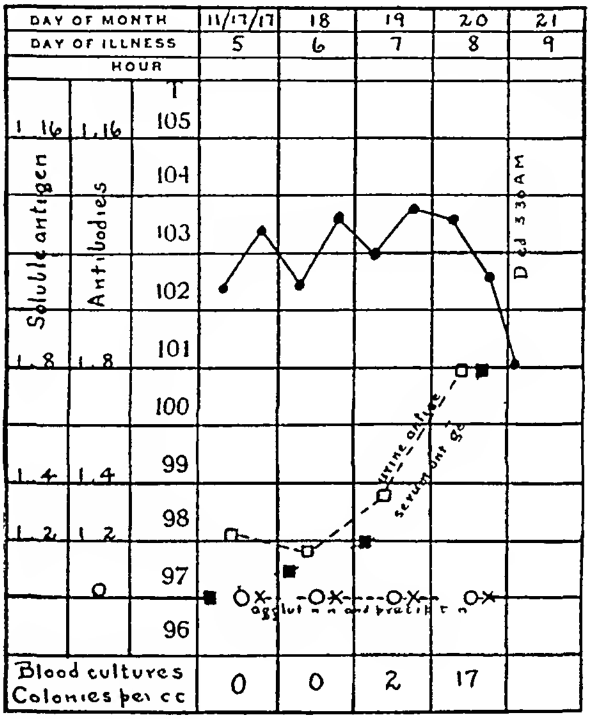

Chart 4—Case A 24 Lobar pneumonia Friedlander's bacillus

antigen by the resolution of the pneumonic consolidation At least it is coincident with it The fact that in two cases during this period small amounts of precipitin in the blood and of soluble antigen in the urine were simultaneously present, is an interesting observation Two theories to explain this phenomenon are presented Antigen and precipitin simultaneously present in approximately equal amounts in the body may not in all instances be completely bound, or the kidney may possess the power of separating the two, excreting the soluble antigen and retaining the precipitin Further study would be necessary to settle this point

On the other hand, in those cases usually severely infected, in which soluble antigen is excreted throughout the course of the disease and in which precipitin does not appear in a free state in the blood, it

would seem probable that the formation of precipitin never equals the elaboration of soluble antigen, which is consequently constantly in excess and readily excreted in the urine That soluble antigen is apparently not present in the blood in these cases probably indicates that the method used for detecting it is not sufficiently delicate when minimum amounts only are present

In general, blood cultures have been negative throughout in the milder cases going on to recovery In severer cases that have recovered blood cultures have been positive early in the disease, but the number of pneumococci per cubic centimeter of blood has diminished daily, the blood becoming sterile coincident with, or twenty-four hours prior to, the appearance of agglutinins The appearance of agglutinins following the disappearance of pneumococci from the blood suggests that here again we are dealing with a struggle between living antigen and its corresponding antibody In those cases in which the development of agglutinins keeps pace with the invasion of the blood stream the pneumococci are kept out of the blood or rapidly removed from it as the agglutinins develop in excess and become demonstrable shortly before crisis That recovery has been invariably accompanied by the appearance of agglutinins is a striking fact That agglutinins have appeared in certain cases (Group II) while a considerable amount of soluble antigen is being excreted in the urine, suggests that the agglutinins may be effective even though the soluble pneumococcus antigen has not been completely neutralized and that their development in excess is essential to recovery from the disease That this is not so with respect to the development of precipitins is evident from the cases considered in the second group The relation between the development of agglutinins and the progress of the septicemia, while not so striking as that between precipitin and soluble antigen, is nevertheless fairly definite This is well illustrated by Case A 29 (Chart 3) in which the disappearance of septicemia is followed by the appearance of agglutinins in the blood and by the fatal cases in which a progressively increasing septicemia with the absence of agglutinins occurs

With respect to the fatal cases, the number studied has been altogether too few to justify any conclusions These cases have been characterized by an increasing septicemia, steady rise in the amount of soluble antigen excreted in the urine, and complete failure to develop either precipitins or agglutinins in the blood These cases alone of the entire series have shown detectable amounts of soluble antigen in the blood, an indication of the overwhelming nature of the infection It is fair to assume that in fatal cases the body is unable to combat the progress of the infection by the production of sufficient antibodies to neutralize and overbalance either the living antigen or its soluble products

The considerations discussed above strongly suggest that natural recovery from lobar pneumonia is largely brought about by the development of a humoral immunity in which agglutinins seem to play an important part Why one individual is able successfully to combat the progress of infection by the development of an excess of immune bodies and another utterly fails to do so, is an intricate question concerned with the factors of varying virulence of the invading organism and varying response of the defensive mechanism of the host about which we possess little accurate knowledge at present Study of the individual case, however, as described in the foregoing, particularly daily estimation of the excretion of soluble antigen in the urine and daily blood cultures with estimation of the number of pneumococci per cubic centimeter of blood, will afford valuable information as to the probable outcome

CONCLUSIONS

While the number of cases studied is too small to establish any final conclusions which may not be subject to alteration with further study, the following facts may be stated with respect to the data obtained

1 There is a definite relation between the excretion of soluble pneumococcus antigen in the urine and the development of precipitins in the blood in lobar pneumonia

2 The development of agglutinins in the blood bears no definite relation to the excretion of soluble antigen in the urine

3 The curve of concentration of precipitins does not parallel the curve of concentration of agglutinins

4 Pneumococci disappear from the blood prior to or coincident with the appearance of agglutinins

5 The balance between antigen and antibody bears a definite relation to the course and outcome of lobar pneumonia, (*a*) in that cases developing an excess of precipitins and agglutinins have invariably recovered shortly after or coincident with the appearance of these antibodies, (*b*) in that cases showing a progressive increase in the excess of antigen without the development of demonstrable antibodies have invariably been fatal

6 Daily estimation of the concentration of soluble antigen excreted in the urine and of the number of pneumococci per cubic centimeter of blood have been of great prognostic value in the individual case

BRAIN CHANGES ASSOCIATED WITH PERNICIOUS ANEMIA *

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The frequency with which symptoms referrable to the central nervous system occur in anemic patients, particularly if the anemia be of the pernicious, or essential type, has long been recognized and made the object of extensive investigation

While our knowledge of this baffling disease has made wonderful strides since Addison first described it in 1855, we have become more and more embarrassed by the seeming increase of our ignorance, and we need be little surprised when we see the chaotic state our problem was in some twenty years later At this time, Schuele,[1] in an excellent study of three mental cases, in which there co-existed a severe anemia, expressed his opinion in this connection by saying "It is apparent, granted that muscular degeneration can be of central origin, that anemias of neurogenic origin also exist," and came to the general conclusion that atrophy of the cerebral cortex was, in his cases, the primary cause of the pernicious anemia Other authors believed the anemia to be the result of some change in the spinal cord

While the object of this study is the investigation of brain changes in essential pernicious anemia, it seems advisable to review some of the more important contributions to the literature on the changes found in the spinal cord in this disease

Although Lichtenstern, in 1884, described two cases of pernicious anemia, complicated by spinal cord symptoms under the title, "Progressive Pernicious Anemia in Tabetics," in which he considered the pernicious anemia to be dependent on the tabes, it was not until 1886 that Lichtheim recognized the real significance of this syndrome, and to him is due the credit of establishing the true relationship of pernicious anemia to subacute combined degeneration of the spinal cord, and of stimulating extensive research in this field, out of which crystallized a great many facts fundamental in neuropathology

While we now have a fairly clear idea of the pathologic processes involved, there still remain a great many problems which require

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1 Bibliography will be found at the end of the article

further elucidation This applies especially to the understanding of the exact mechanism by which these changes are brought about Although there are still some writers who consider the anemia to be the chief factor in causing the degenerations of the spinal cord (Goebel), most writers have come to the conclusion that it is really a toxin, or several toxins which must be responsible for these alterations (Minnich, Nonne, Petren, Von Voss, Russell, Batten and Collier, Johnson, Reuling, Bonhoeffer, etc)

That toxins alone are able to produce such changes, we know from the alterations which occur in the cord, which in many cases cannot be distinguished from those associated with pernicious anemia, when various poisons are introduced into the human organism, the same changes also appear as a result of certain poisons and in connection with certain morbid states, that is, lead, arsenic, ergot, pellagra, lathyrism, chronic alcoholism, diabetes, leukemia, severe secondary anemias, diphtheria, Addison's disease, tuberculosis, syphilis, typhoid, carcinoma, senility, chronic jaundice, malaria, leprosy, influenza, scarlet fever, tetanus, pregnancy, shock and tea (Gordon)

It was also pointed out that the nervous symptoms may precede the appearance of the anemia, sometimes by many months, which made the view that anemia alone might be the cause untenable (Minnich, Nonne, Bastianelli, Van Wart)

The fact that patients, having pernicious anemia, often have an elevation of temperature, was also taken to indicate that a toxin was at work (Lloyd) Von Voss, however, furnished the best evidence when he induced an anemia in laboratory animals by injecting pyrodin, glycerin, pyrogallol, and toluylendiamin, with the result that only one animal showed cord changes, and these were different from those occurring in pernicious anemia, no changes, analogous to pernicious anemia in the human, were found in these animals Thus, anemia, per se, cannot be the cause of these lesions, the real cause, probably, being a toxin

That the toxin, and not the anemia alone, is responsible for the cord changes, has thus become the generally accepted theory As to its source, nature and mode of action, however, we are still completely at sea If we were to accept Naegeli's view, that pernicious anemia is always a toxogenic anemia, coming from a variety of sources, notably such as the Bothriocephalus, pregnancy, syphilis, and malaria, and that a pernicious anemia may in reality, therefore, at times be a secondary anemia and amenable to treatment, the problem would become greatly simplified His definition, however, is not accepted by all writers, and many, perhaps most of them, insist that a true pernicious anemia must be essential, or idiopathic, and some add, fatal, and that therefore, any

demonstrable etiologic factor would at once place it into the class of secondary anemias This leaves us in a difficult position Nonne evaded this difficulty by substituting the term "lethal anemias"

It may be in order here to remark that this looseness in the terminology must be kept in mind in reviewing the literature, and in interpreting the necropsy reports Thus, for example, we again and again find syphilis present in the cases reported under the caption, "pernicious anemia", the findings in such cases are obviously rather hazardous to interpret

For this paper, therefore, I have used only such cases of anemia as would be classed under the term "primary idiopathic" With this slight digression, we can again turn our attention to a brief consideration of the theoretical toxin, or toxins, at work

Minnich was the first to suggest that this toxin might be of gastro-intestinal origin, more recently attention has been directed to the tonsils and teeth

Blankenhorn, in a clinical study of the blood serum of pernicious anemia patients, made the observation that those patients, in whom the serum yielded the strongest Pettenkoffer reaction, showed, clinically, the greater involvement of the central nervous system He, therefore, concluded that it was the presence of large amounts of bile salts in the blood that was responsible for these neurologic manifestations

Our understanding of the mode of action of these toxins is little better According to a good many authors it is but one toxin that is responsible for both the blood vascular changes, so frequently observed, and the neuronal degeneration (Johnson), others regard it as more selective in its properties, and consider this specificity, plus a difference in resistance, inherent in various structures of the central nervous system, as an explanation of the localization of the destructive process (Russell, Batten and Collier), still others insist that there must be at least two separate and distinct toxins at work, one having an affinity for the red blood cells, the other, an affinity for the fibers of the spinal cord (Reuling)

Von Voss, in discussing this phase of the subject, does not come to any such definite conclusions, but leaves the question *sub judice,* the changes may accordingly be due, (1) to one toxin causing both the anemia and the cord changes, (2) the toxin may be indirectly produced by the anemia, and then bring about the changes in the spinal cord, and (3) the anemia itself may act as a toxin, which through malnutrition causes the alterations in the cord

The second hypothesis, in a slightly altered form, is also advanced by Bonhoeffer, who, in discussing the psychoses occasionally observed in pernicious anemia patients, does not consider these specific reactions

as due to a toxin, but supposes other changes in the brain cells themselves or in their metabolism to be interposed — a view gaining increasingly wider acceptance in analogous conditions, as, for example, between alcohol and delirium tremens, as opposed to alcohol and drunkeness

That the lesions found in the central nervous system are the result of toxin action can hardly be questioned, nor can it be doubted that anemia in itself can and does render the nervous elements more susceptible to the actions of these toxins Any further statements are purely hypothetical and unwarranted on the basis of our present knowledge

A most animated discussion has been that which centered around the pathologic mechanism, instrumental in producing the so-called Lichtheim foci and the subsequent condition of combined sclerosis According to the first theory advanced, it was the blood vessels which through hyalinization, thrombosis or rupture, were considered responsible for these lesions

Minnich, in a series of five cases of pernicious anemia, free from neurologic symptoms clinically, and which subsequently came to necropsy, found no lesions whatever in the nervous system, other than multiple hemorrhages, which he studied in great detail These he considered fundamental in the production of the Lichtheim foci, and believed them analogous to the multiple hemorrhages occurring in the retina, pleura, pericardium, intestinal serosa, and meninges As to the alterations taking place in the vessel walls themselves, he assumed the process to be initial in the perivascular lymph spaces and supporting tissue, with resulting lymph stasis, perivascular sclerosis, intimal thickening, vascular sclerosis, and consequent tissue destruction Nonne's views were essentially the same

While probably the majority of writers, among them Burr, Bullock, Johnson and Marburg, mention vascular changes, such as proliferation and swelling of the intimal cells, hyaline degeneration, and often complete thrombosis, their conclusions are not the same

According to Marburg, the localization of the pathologic process in the cord, corresponds to that area which is best supplied by blood vessels, and hence has transported to it the largest amount of toxin Curiously enough, Brauwer and Blaukwip reverse this statement, saying that not the areas best supplied with blood, but those most poorly supplied, are the ones which suffer most extensively Schmaus, here, as in multiple sclerosis, is a supporter of the lymph-stasis theory

While the "vascular theory" was for a time widely accepted, it did not long go unchallenged It was pointed out that not only did the blood vessels in the diseased areas too often look normal, but also

blood vessels in healthy areas too often were much diseased (Bastionelli, Russell, Batten, and Collier, Jacob, Moxter, Von Voss, Putnam and Taylor) It was likewise shown that in a great many cases there was no evidence, whatever, of hemorrhage (Russell, Battèn, and Collier)

Relative to the lymph stasis theory, Lenel suggests that the swelling seen in the adventitial tissue may be only a stage in the "Abbauvorgang," and thus a result, rather than a cause, of the nerve lesions

An entirely different explanation is advanced by Rothmann, who found hemorrhages, atrophy, and destruction of the anterior horn cells in the gray matter These, he argues, as does Teichmueller, are the changes which initiate the cycle of disintegration, while the alterations seen in the white matter are due simply to a resulting secondary degeneration He insists further, that although these lesions are not always demonstrable microscopically, the injury is there nevertheless, and the mechanism the same

Goebel, on the other hand, though he also demonstrated changes in the gray matter, refutes this idea by saying that the changes in the gray matter are often missing, that the intensity and the localization of these changes do not correspond with those found in the white columns, and that in longitudinal sections, the commissural fibers are found to be intact Additional evidence was supplied by Bastionelli, who noted that the white fibers were diseased only in the peripheral portions of the cord and that the gray matter, for this reason, could not be the primary seat of the degeneration

On account of the evidences of inflammation sometimes observed, and the occasional febrile course, it is thought by some (Boedeke and Juliusberger) that the process taking place here is really a true myelitis of the disseminated type This, Nonne thinks, is also true of sepsis and senility The fact, however, that inflammatory reaction, such as cell infiltration, is too often lacking, and that the gray matter is only exceptionally involved (Billings) argues against this view

Edinger, in support of his "Ersatztheorie" performed an experiment which has a direct bearing on the point under consideration In the spinal cords of a number of rats, in which he produced an anemia, and which he then set to work by the ingenious device of suspending them by their tails, he found extensive degenerative changes, while in the cords of control rats, which were not anemic, no such changes could be detected

Finally, Dana has emphasized two other factors, which may be at work in this disease and which may be instrumental, first, in determining the characteristic localization, and, second, in deciding which patients are to get a combined sclerosis, and which are to remain

altogether free from it It is in reality the peripheral ends of the axones of the pyramidal cells and of the posterior ganglion cells that bear the brunt of the destructive process, this, he says, may be due to the distance of this portion of the nerve fiber from its trophic center Relative to the second point, he suggests that this may be explained by individual predisposition, that those persons hereditarily endowed with "weak cords" will be the ones to suffer from a complicating cord degeneration, while those who were not so predisposed, will escape

A not infrequent finding in the spinal cords of pernicious anemia patients is the presence of cavity formation (Baumler, Camac and Milne, Bullock, Friedlander, and Henneberg) Boedeker and Julius-berger described peculiar stafflike structures as occurring, associated with a few of the anterior horn cells, these were at times scattered throughout the entire cell, at times in only a portion of it, then again partly within the cell and partly in the pericellular space, and sometimes entirely within the latter These structures, stained green with iodin, red-brown with basic fuchsin, were present in the Marchi sections, and remained unstained with methylene blue, eosin, and hematoxylin

While the foregoing is a rather fragmentary and disconnected review of this aspect of pernicious anemia pathology, it is not the object of this paper to enter on a discussion of the many theories advanced, save only in so far as may be necessary to explain the pathologic changes noted in the cortex

The literature bearing on the clinical manifestations of cortical origin is not so voluminous as is that concerning the spinal cord, however, in recent years, attention has been directed this way, and numerous cases, in which psychotic manifestations were noted, have been placed on record Already Addison, in 1855, when he first described the disease, spoke of the occasional wandering of the mind, and, indeed, a terminal delirium, usually of a mild type, is one of the commonest of the mental phenomena noted There appears to be no law according to which these disturbances develop, and the psychic alterations may run the entire gamut of mental symptomatology

In cases which develop some of the better defined types of psychoses, such as manic depressive insanity, it is probable that an individual predisposition was present, the pernicious anemia being really more or less independent of the mental disorder, when this has not been the case, however, the majority of writers have come to the conclusion that the individual may be altogether free from any neurotic tendency, the psychosis being then placed in the category of the exhaustion (Bonhoeffer, Meyer) or infection-intoxication psychoses (Siemerling)

Putnam and Taylor consider a neurotic tendency fairly common, and noted in their patients, as a rule, an exaggeration of native traits. Church describes the mental condition as one of a continuation of the dream state, which these patients cannot shake off on being roused and which usually subsides spontaneously on further stimulation. Picket, from a study of seven cases, gives the composite mental picture of these patients as a shallow confusion with impairment of ideas of time and place, increasing on awakening from sleep; illusions, particularly of identity, are common. Hallucinations and persecutory delusions may arise. "The pernicious anemia is mainly an abeyance of the mind." Very often the psychosis may simulate a general paresis (Marcus, Camp), Korsakow's syndrome has also been noted following a delirious condition (Bonhoeffer).

Just as cord symptoms may appear long before there is any evidence of the underlying pernicious anemia, so mental symptoms may appear in persons who may be somewhat anemic, but in whom the diagnosis of pernicious anemia would not be warranted. This was well shown in a case reported by Marcus, and also emphasized by Langdon, who in a series of cases, some of the patients having definite pernicious anemia, others having more or less severe anemia, designated the condition as "pre-pernicious anemia." Likewise, these symptoms are strikingly transitory, and usually improve, *pari passu,* with an improvement in the physical state (Grawitz).

Kraeppelin, although he discusses the relation of anemia to psychoses at some length, does not mention pernicious anemia in particular, and concludes by saying that it is not clear whether the anemia is a causative factor or an accidental accompanying condition.

The contributions of Barrett are particularly illuminating. Among 650 necropsies on insane persons in Michigan, he reports that there were fifteen cases of pernicious anemia, and suggests that this disease may play a larger rôle in psychiatry than is now supposed. In his first study of nine cases, two resembling dementia praecox, one manic-depressive insanity, and six asthenic with paranoid feature, he concluded that, as a whole, these patients had in common, irritability and suspiciousness, which formed the groundwork for delusions of persecution, the content of which was generally influenced by the somatoneurologic symptoms. In several cases hallucination and confabulation occurred, suggesting a Korsakow's psychosis. There was no marked deterioration, and comprehension and orientation were usually clear, except for a rare episode. In two instances there was slight expansion. In a number of cases there were remissions in the mental condition which ran parallel to those on the physical side. In all but one there was a hereditary predisposition, which he regards as of considerable

importance He classifies these cases among the paranoid conditions which are symptomatic of a toxic-organic process affecting the central nervous system, analogous to those found in tabes, alcoholism, and certain drugs intoxications

Only a few of the cases reported present symptoms referable to other parts of the central nervous system, outside the cord Among these optic atrophy stands first and has been several times noted (Russell, Bastionelli, Putnam and Taylor, Bramwell) Collier, however, declares it to be a decidedly uncommon occurrence, having been found but once in fifty-eight cases, and in this one instance, being probably of syphilitic origin

Various attacks of cortical origin have been described, such as a sudden feeling of cold and death in an extremity (Eichorst), light hemiparesis of the face (Immermann), passing hemiplegic attacks (Mueller, Nonne), which may be accompanied by convulsive seizures (Mueller and Bierner), diplopia (Russell, Batten, and Collier), sudden severe headaches (Hawthorn), and total blindness from extensive softening of the occiptal lobes (Wicher)

As to the pathologic lesions found in the brain itself, comparatively little has been published Birulja, in 1894, found numerous small blood extravasations, accumulations of lymphoid cells, pigment masses, and diminished tincture with carmin Ransohoff noted inflammatory foci in the brain and cord Mott described marked changes in the corticopyramidal cells, and on examinations with the Marchi method showed degeneration in the whole pyramidal system, from the cortex downward Spiller, however, takes exception to this diagnosis and looks on it as a case of amyotrophic lateral sclerosis, associated with anemia This author found changes as high as the middle of the pons, which he considered retrograde Preobrajensky has described two types of foci occurring in the medulla, cord, and cerebellum—1, miliary sclerotic foci accompanying the blood vessels, and 2, miliary foci from disintegreation of the nerve substance

Schroeder regularly finds miliary foci occurring in the brain in lethal anemias, not found in other diseases These differ somewhat from the Lichtheim foci and are usually about 80 to 100 microns in diameter, globular or slightly oblong, always isolated, and generally widely separated from each other, they are in close relationship to the blood vessels, each one having a capillary in its center, and display no selective localization They are most readily found in Nissl-stained sections, in which the center appears clear, containing sometimes a few blood cells, and the periphery blue, being made up of more or less degenerated glia cells These "Ringwallherdchen" have no relation to the plaques found in the spinal cord

Barrett has reported findings in eleven cases, which are exceedingly interesting. The Nissl bodies he found often markedly disintegrated, a few cells showing the characteristic axonal degeneration. The neuroglia cells were, as a rule, moderately increased and had a tendency to group arrangement; in some of them mitotic figures were noted. Rod cells and cells of odd shapes were present in the cortex in considerable numbers. Degenerative changes in the blood vessels and pigment deposit were common. The striking finding, however, was that of typical Lichtheim placques in four of the eleven brains examined, ten of which showed distinct pathologic changes. These changes, he concludes, were such as occur in conditions of chronic intoxication and resemble those found in chronic alcoholism. He also found in one of the brains (Case 2, M. T.) the foci described by Schroeder.

Pfeiffer, in a very careful histologic study of the cortex, found a good many cellular changes, the most frequent of which was swelling of the ganglion cells, invariably associated with hyperpigmentation. These changes are similar to those found in psychoses of toxemic origin.

REPORT OF CASES

Seven brains, in all, were available for study. These had been fixed in formaldehyd solution and were now cut in the frontal plain so as to obtain sections about 8 mm. in thickness through the entire brain, from each of the following levels: (1) section just anterior to the genu of the corpus callosum; (2) section 0.5 cm. posterior to the optic chiasma; (3) section through the center of the cut surface of the crura cerebri, the cerebellum and pons having been removed; (4) section cutting through the posterior end of the splenium corporis callosi; (5) section through the middle of the pons and that portion of the cerebellum overlying it; (6) section through the medulla and the cerebellum at the middle of the olive. These blocks were then mordanted, imbedded in parlodion—celloidin being practically off the market—cut under alcohol, by means of the large Edinger microtome, into sections 50 to 100 microns in thickness, and stained by the Weigert and the Pal-Weigert methods, the Van Giesen counterstain being added to some of them.

Since the Weigert sections of four of these brains showed marked evidences of disease, frontal sections cutting through the entire brain at levels corresponding to the Weigert sections were also prepared and stained with osmic acid according to the method of Marchi; supplementing these, Marchi sections were also prepared from certain other areas of these brains. The Marchi sections from the remaining three brains, while not cutting through the entire brain, were sufficiently large and numerous to permit a careful and satisfactory study. Silver sections were prepared by the Bielschowsky method, the pyridin modification for the preparation of serial sections as well as the method described for frozen sections, being employed. For general histology and cell study, representative areas of the cortex were stained by means of hematoxylin and eosin, thionin, toluidin blue, and neutral red. The *Lichtgruenfuchsin* stain, devised by Alzheimer, was employed for the demonstration of fuchsinophilic granula. Glia fibers and cells were studied by means of Weigert's glia fiber stain and the new gold stain recently developed by Raymón y Cajal. The larger blood vessels at the base were stained with hematoxylin and eosin and with Weigert's elastic stain in various combinations.

CASE 1 —(Necropsy 14-113) *History*—The history shows the following G M, 51 years of age, married, traveling salesman and a blender and taster of wine for twenty-five years, presented himself for examination Dec 4, 1912 His father died of heart trouble at the age of 42, and his mother of stomach trouble at the age of 62 One brother and two sisters were living and well His general health was good up to the age of 40, with the exception of a nervous, rundown condition for two or three months when he was 15 years old, during which time he was not confined to bed and from which he recovered completely He also had measles, whooping cough, and was rather ill with chickenpox There was no diphtheria, scarlet fever, pneumonia or typhoid Syphilis and gonorrhea were denied Up to fifteen years previous to the examination he used considerable wine and whisky, but since that time had been more moderate He had always been a rather hard worker He married at 22, had one child, and his wife had one miscarriage, due to accident He was married again at 33, there being no pregnancies during the second marriage Eighteen years previously he received a slight injury to his back, which pro-

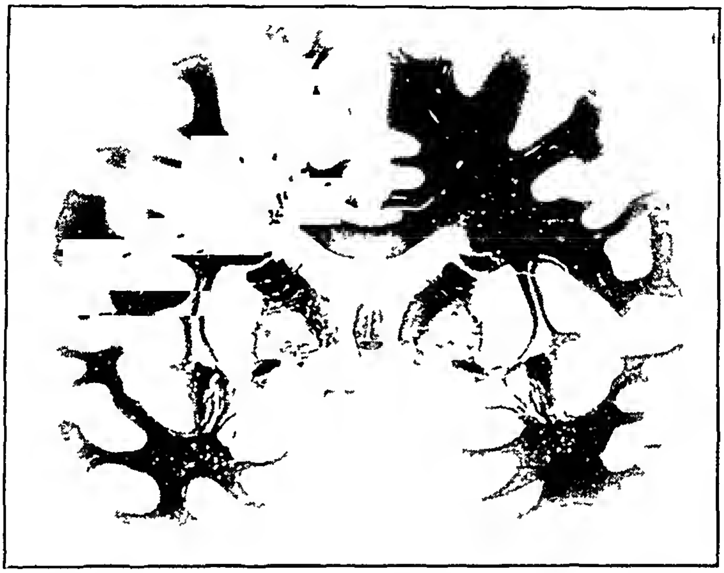

Fig 1 (Case 4) —Weigert's myelin sheath stain Cross section of brain, showing gross appearance of degenerative foci, analogous to the so-called Lichtheim plaques occurring in the spinal cord in cases of pernicious anemia

duced no symptoms at the time About this time he also was considerably jaundiced and complained of pain and tenderness over the gallbladder region He suffered a good deal from indigestion, but this bothered him little during the last four or five years He also has been constipated for years His present illness began in January or February, 1914, during which time his legs became easily cold and would ache, mostly in the shins and feet This ache was sharp rather than dull, and was present especially when cold He gradually began to get stiff in the legs, this at first caused no trouble in walking, but later on the toes began to catch About three months previously he experienced some tightness about the waist, which was now largely gone Two months previously he began to stagger in walking, which increased until about a month and a half previously, since when he had been unable to walk alone For the previous two weeks there was also some drawing in the legs, together with a sensation of burning in the legs and buttocks At this time he was said to have been rather pale For one week or more he had some difficulty in urination, which began with sharp pains in the scrotum, the water was slow to start and dribbled at the last He also had considerable difficulty in getting his bowels to move

Of late his appetite had not been very good He always felt much worse in cold than in warm weather For the previous two days there had been some edema of the left ankle His color was fair, but growing somewhat pasty

The systolic blood pressure taken on the day of examination was found to be 116 mm Hg

Neurologic Examination —The neurologic examination showed the following *Cranial Nerves* The sense of smell was found to be normal when tested with perfume Vision was practically normal and the field of vision was good to a rough test There was no central scotoma Fundus examination was not very satisfactory but the eye ground appeared to be normal in the right eye There was no diplopia, no nystagmus, and movements of the external occular muscles were normal The pupils were circular, the right being a little smaller than the left Reaction to light was rather sluggish and reaction to accommodation normal Functions of the seventh and eighth nerves were normal, as were also the tuning fork tests Sensation over the distribution of the fifth

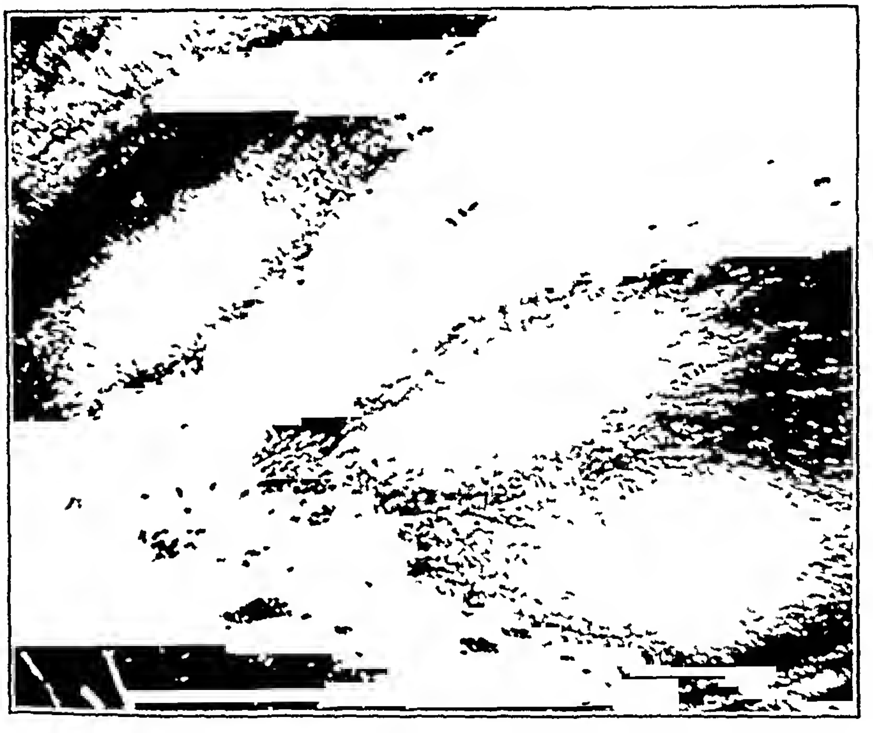

Fig 2 (Case 4) —Weigert's myelin sheath stain Lichtheim type of focus present in the corpus callosum Magnified about 20 diameters

was normal, save that the conjunctival reflexes were sluggish The ninth, tenth, eleventh, and twelfth cranial nerves were normal The speech was a little peculiar, however, it was probably always so *Muscles* There was some jerking of the legs, each jerk being accompanied by a sharp pain The patient stated that this jerking was always aggravated when he became cold or very hot The dynamometric test of the hands registered about 38 on the right and 30 on the left The abdominal recti were normal In the legs there was moderate weakness of the anterior thigh group on the right and great weakness on the left The anterior tibial group was normal on the right but impaired on the left Power in the calf muscles was poor on both sides There was no special tremor of the extended fingers *Reflexes* The deep reflexes of the arm were a little below normal The abdominal reflexes were all missing except twice, when a slight response in the right lower abdomen was obtained The scrotal reflex was absent Both knee kicks were very active There was a double ankle clonus of rather short duration, somewhat better sustained on the left than on the right Scratching for the Babinski reflex was decidedly painful on the

right, less so on the left the left plantar was constantly extensor, the right was at first flexor and then extensor *Sensation* The patient said that he could feel the clothing on his feet and cutaneous sensation was practically normal everywhere except for some slight impairment on the plantar surface of the toes of both feet and over the left shin Subjectively, there was some numbness and prickling in the hands which was worse when he became cold The patient said that at times he did not know where his legs were, though he had an appreciation of the movement in his toes when wiggling them Joint sensation in the toes was completely absent when tested objectively and impaired to a considerable degree in the ankle Vibration sensation in the legs was normal All stroking of the abdomen and chest with a dull instrument was painful Coordination in the hands was fairly satisfactory, though there was a little awkwardness in handling things In the legs there was distinct ataxia Stereognosis was normal

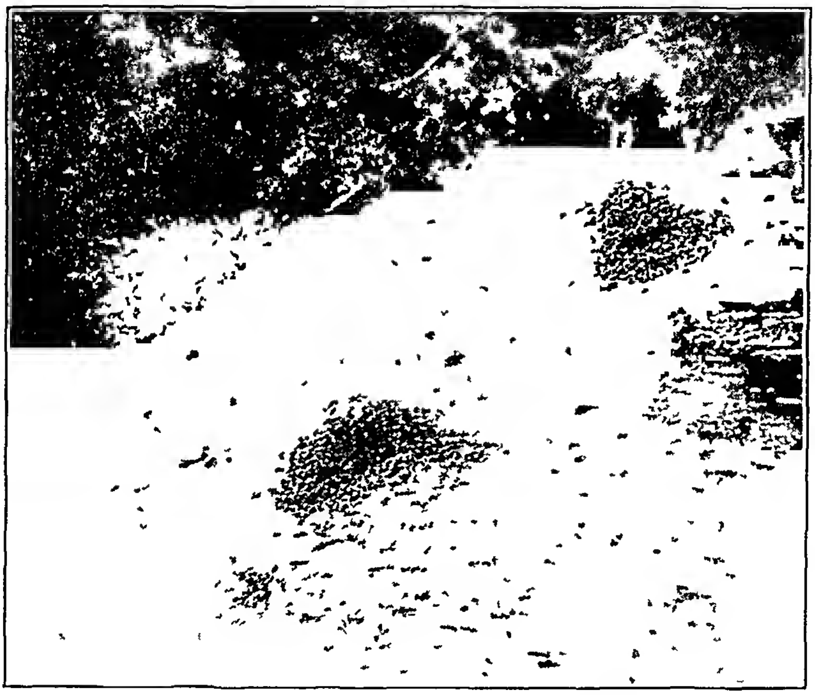

Fig 3 (Case 2) —Weigert's myelin sheath stain, Van Gieson counterstain Plaques of degeneration found in the centrum semiovale, crus level The one seen in the upper left hand corner is of the "palm-tree" type, in which the degeneration occurs at the point of bifurcation of a capillary

Course—Jan 1, 1913 The patient complained of some numbness and stiffness in the hands and arms Practically all the swelling of the left foot and leg had disappeared The patient said that he could pass water into a cold urinal, which he could not do before

Jan 19, 1913 The pupils were a little small and reaction to light and distance was normal Both legs jerked considerably The deep reflexes of the arms were rather sluggish The upper and lower abdominal reflexes were faint and the right was soon exhausted The cremasteric reflexes were absent Both Achilles tendon reflexes were active There was a slight patellar clonus on both sides, as well as an easily exhausted ankle clonus, which was somewhat better on the left than on the right There was a distinct Babinski phenomenon on the left, while on the right the plantar reflex was at times extensor, though usually flexor There was possibly a slight disturbance of tactile sensation from the seventh rib downward, though there was no disturbance of pain sensibility,

save possibly in the feet, where he often called the head of a pin the point The patient was sensitive to tapping and stroking of all parts of the body Joint sense in the hands seemed to be normal The patient said that he still lost his legs at times, though he could usually tell when one leg was on top of the other, and which it was Joint sense in the toes was almost completely lost Vibration sensibility was present over the malleoli and over the shins

Feb 5 1913 The patient raised his legs from the bed fairly well, though the left was somewhat weaker than the right The deep reflexes in the arms were not increased Both patellar reflexes were very active, there was a patellar clonus present on the left and a very faint patellar clonus on the right There was a slight double ankle clonus of short duration The Babinski phenomenon was positive on the left and doubtful on the right Bowel and bladder control was good

Fig 4 (Case 4) —Weigert's myelin sheath stain Another illustration of the relation which these plaques sometimes bear to blood vessels This particular one was present in the fibers of the optic radiations

June 7, 1913 The patient was getting out of doors and walked with the assistance of a cane and the occasional support from a building His legs were very stiff He had never been quite wholly free from the prickling sensation and thought that it was a little worse of late The grip of the right hand registered 45 and of the left 35 The right plantar response was flexor and the left doubtful There was no clonus On the plantar surface of the right index finger he felt pin pricks a little less distinctly than on the left side The blood pressure was 154 mm

June 22, 1914 Last winter the patient grew considerably worse and did not improve much during the summer He began failing mentally, was extremely irritable and unreasonable, and several times struck at his wife He had had distinct spastic phenomena and a good deal of sensory impairment When seen two days ago there was distinct hypotonia and no clonus could be obtained. He ultimately became very stupid and died without any special further change

Necropsy—Death occurred June 22, 1914, a necropsy being performed while the body was still warm The necropsy protocol was as follows

The body is that of a well developed, well nourished man, 168 cm in length There is slight rigor mortis in the upper extremities Lividity is present in the dependent portions The pupils measure 5 mm in diameter and are equal There is no edema A few small ulcers are present on the posterior surface of the sacrum The peritoneal cavity contains no excess fluid The subcutaneous tissue anteriorly is 2 5 cm in thickness The appendix is 12 cm in length and is bound down by a few old adhesions The diaphragm extends to the fourth intercostal space on the left and to the fourth rib on the right The pleural cavities show small fibrous adhesions at the base of the right lung with no excess of fluid in either cavity The pericardial cavity contains no excess fluid The heart is normal in size, the epicardium and endocardium are clear and smooth, and the valves thin and soft The myocardium is of a pale reddish color and fairly firm The root of the aorta shows no gross lesions The

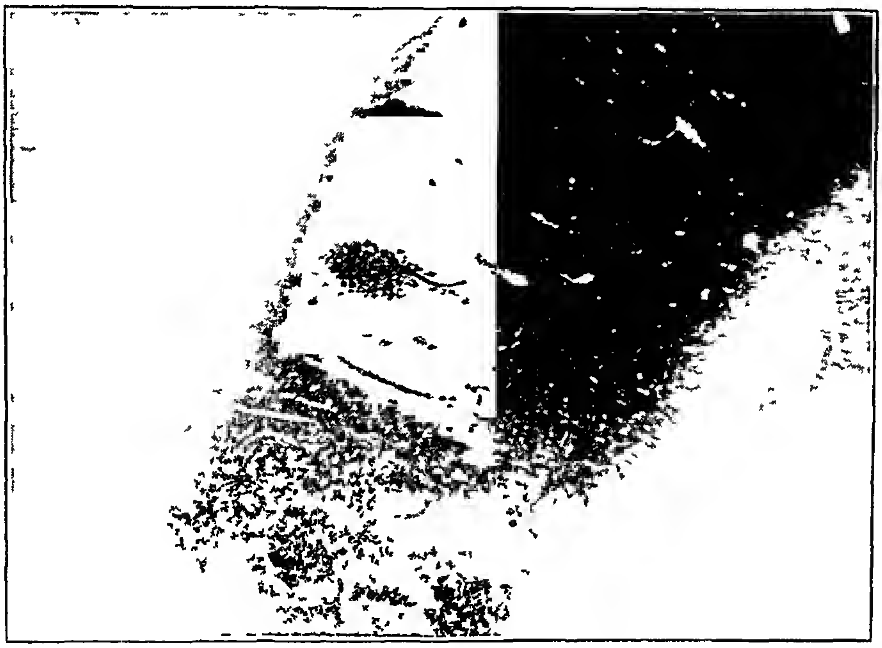

Fig 5 (Case 2) —Weigert's myelin sheath stain Lichtheim focus, associated with a small blood vessel, present in the brachium conjunctivum

lungs crepitate throughout and the posterior portions are somewhat heavier than the anterior The cut surfaces show a small amount of bloody, frothy exudate In one area of the right lung, a small amount of pus can be expressed from the bronchioles No nodules are palpable The spleen shows a slightly wrinkled capsule The cut surface is of a reddish color and fairly firm The pulp scrapes with some resistance No special markings are visible The liver is somewhat smaller than normal, the capsule is smooth and clear, and the cut surface shows no special features The pancreas and gastro-intestinal tract appear normal The adrenal shows no gross lesions The kidneys are of normal size The capsules strip with a little resistance The cortices are about normal in thickness and the demarcation between the cortex and the medulla is fairly sharp The bladder and genital organs were not removed On removing the dura mater, the subarachnoid space is found enormously distended with a thin clear fluid The arachnoid is thin and translucent The arteries of the brain are soft No pathologic condition is present in the brain substance from external examination The subarachnoid space of the

cord is distended with a thin clear fluid Sections of the spinal cord in the cervical, thoracic, and lumbar regions show areas of degeneration in the white substance which are rather diffuse, except in the cervical region where the column of Goll is sharply circumscribed and degenerated The bone marrow from the central part of the shaft of the right femur is of a yellowish white color In the upper third of the femur, near the posterior portion, the marrow is found to be of a deep red color

Microscopic Examination—The heart shows several small areas of fibrosis The lungs and adrenals appear normal The liver shows a marked atrophy of the hepatic cords with a small amount of pigment There are also evidences of a slight chronic passive congestion The kidney shows a few small patches of fibrosis near the capsule, but is otherwise normal The spleen shows some atrophy with a hyaline degeneration of the arterioles In the spinal cord the majority of fibers of the white columns are degenerated, this is especially marked in the posterior and lateral columns, those fibers which are in con-

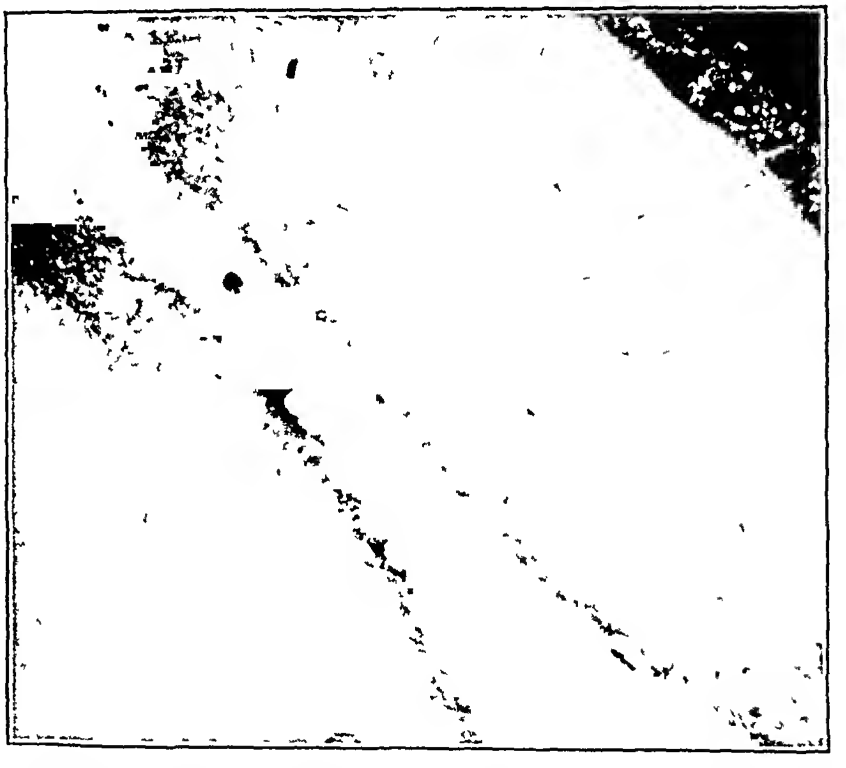

Fig 6 (Case 2) —Weigert's myelin sheath stain Gyrus fusiformis, showing the small circular foci found in the medullary substance just underlying the marginal gray layer, corresponding probably to miliary foci described by Preobrajensky

tact with the gray substance are not degenerated The bacteriologic examination of the heart's blood shows no growth A smear made from the pus expressed from one of the bronchioles shows bacteria of various kinds The anatomic diagnosis was as follows 1 Combined sclerosis of the spinal cord, 2 edema of the brain, 3 pernicious anemia (?)

Examination of Brain—The brain is of normal size and rather pale The membranes are somewhat opaque along the blood vessels and show some edema The convolutions are normal in appearance The blood vessels at the base are moderately thickened and slightly tortuous A few slight atheromatous patches are also noted

Weigert Sections *Sections through the frontal lobes* On the right side of the brain, a little above the midline, and well within the substance of the

centrum semiovale, are a dozen or so irregular areas, about 0 5 mm in width and 1 to 2 mm in length, in which the white fibers do not stain These areas are associated with capillaries which they sometimes surround concentrically, though more often lying somewhat or altogether to one side, the edges are irregular and ill defined and there is a distinct tendency for the degenerated areas to spread in the direction of the fibers *Sections through the level of the chiasma* Grossly there is seen a small triangular area of degeneration in the upper portion of the lenticular nucleus, in the angle between the internal and external capsules, also a smaller area in the upper and outer portion of the caudate nucleus Areas of degeneration, similar to those described above, are seen in great numbers in both semiovale areas, though somewhat more on the right than on the left, in the corpus collosum, and in the optic tract near

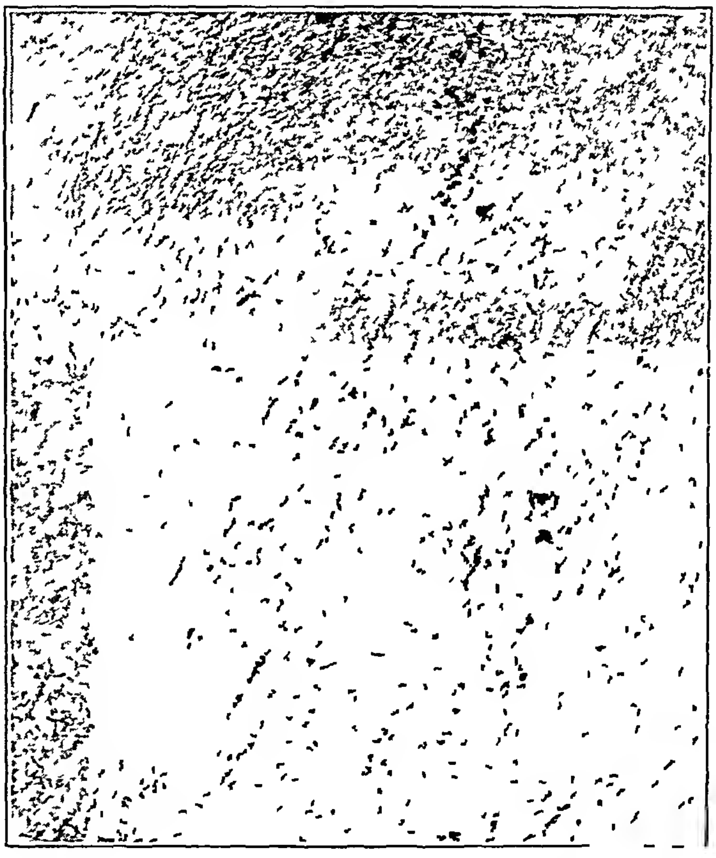

Fig 7 (Case 4) —Marchi stain × 50 An area of degeneration, constituting possibly an early stage in the production of a Lichtheim plaque Second temporal gyrus

the chiasma *Sections through the level of the crus* With the unaided eye one can see a sharply defined, wedge-shaped area of degeneration, the base of the wedge being directed upward, which involves the outer quarter of the putamen The upper and outer portion of the caudate nucleus shows a similar degeneration about the size of a pea Areas of perivascular degeneration appear scattered throughout the white matter They are more numerous on the right side, where there are some twenty in number, than on the left, and are also seen in number, in the corresponding area on the left, in the corpus callosum and in the fornix Under the microscope these changes are found to be more marked around the smaller blood vessels than around the larger ones, marked ballooning of the myelin sheaths is seen, particularly at the periphery of some of these areas *Sections through the occipital lobes* The same areas of degen-

eration appear but are less numerous than in the preceding section They are particularly numerous in the corpus callosum and in the fourchette, although they occur in smaller numbers in all other portions of the white matter In the marginal gray layer of the gyri is seen, surrounding some of the blood vessels, a distinct halo *Sections through the cerebellum* Under the dentate nucleus is found an area of perivascular degeneration similar to those described above *Sections through the pons* In the left brachium conjunctivum is a typical Lichtheim focus with marked ballooning of the fibers A similar but somewhat smaller focus is seen in the left brachium pontis Other structures in this section appear normal

Marchi Sections *Sections through frontal lobes* The sections show a rather diffuse degeneration of moderate intensity with some accumulation of pigment in the perivascular spaces There are also seen a number of relatively pale areas with poorly defined margins, surrounding some of the blood vessels The corpus callosum shows no more degeneration than is found in

Fig 8 (Case 1) —Marchi stain ×50 Area of extensive degeneration in centrum semiovale, level of the crus

other portions of the section The pyramidal cells are all rather more deeply pigmented than is normally seen *Sections through level of chiasma* There is a diffuse, rather marked degeneration throughout the white matter of the section, which is particularly prominent in the fibers passing from the surface toward the internal capsule Small, circular, pale areas, which are rather sharply defined, appear in moderate numbers in both the marginal gray and the submarginal white matter The pyramidal cells of the cortex appear normal *Sections through level of crus* Here are seen very numerous foci, formed by deposits of blackened granules, most of them having a definite relation to the blood vessels, these are particularly numerous in the centrum semiovale, where the degeneration is very intense As the crus is approached, the degeneration is seen to be older, on the whole, though recently degenerated fibers are scattered throughout Although the degeneration is most marked around the blood vessels, the intervening areas also show a considerable disintegration of the

nerve fibers That portion of the cortex occupied by fibers of the optic radiations, also shows a marked deposit of small and somewhat dusty granules All stages of degeneration can be followed in various parts of the section The primary ballooning and browning of the fibers, the formation of Elzholz corpuscles, chains of coarse black beads, disintegration of these into finer granules, and their transport in "Abbauzellen," to the perivascular spaces The pyramidal cells which overlie these areas contain no more than the normal amount of pigment The basal nuclei are normal in appearance, save for the accumulation of a small amount of perivascular pigment *Sections through occipital lobes* Grossly one can see pale areas, presumably perivascular, which appear somewhat as was noted in the Weigert sections The degeneration of this portion of the cortex is well marked and most intense in the fibers of the optic radiations and of the corpus callosum As in the preceding sections, all stages of degeneration can be noted Perivascular areas of degeneration are seen here and there, together with varying amounts of fatty accumulations The pyramidal cells here are rather markedly pigmented, particularly in the lower

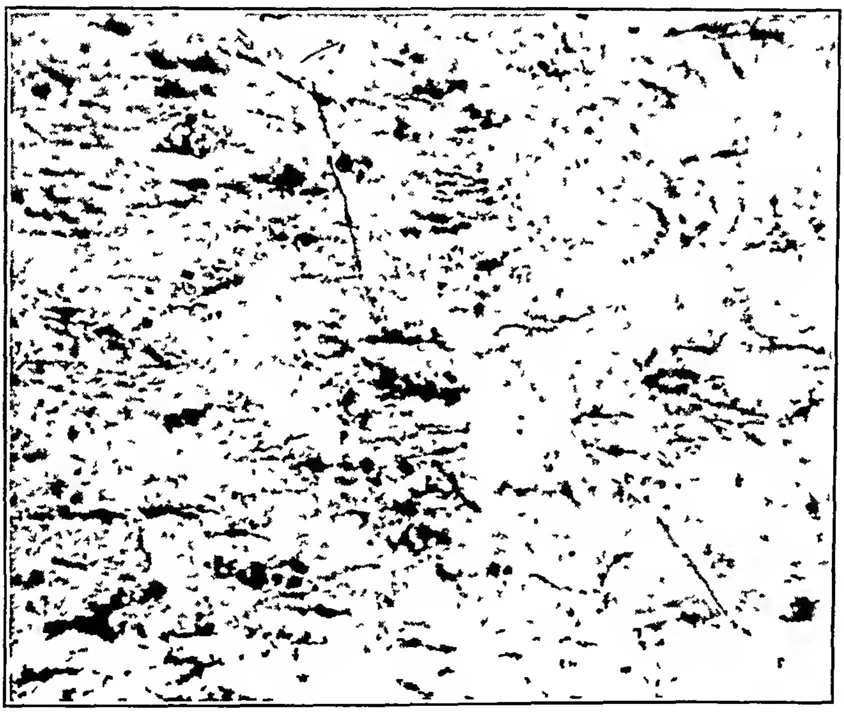

Fig 9 (Case 1) —Marchi stain × 100 Portion of Figure 7, under higher magnification

portion of the occipital lobes, some of the cells, and this is notably true of those in the third pyramidal layer, being in many instances completely replaced by pigment There appears to be no definite relationship, however, between the degree of hyperpigmentation of these cells and the degeneration of the fibers underlying *Sections through olives and the overlying cerebellum* There is a rather diffuse degeneration noted throughout the white matter of the section In the cerebellum this is particularly marked in the peduncle of the flocculus and in those fibers which descend from the dentate nucleus, where the evidences of degeneration are marked In the cross section of the medulla, degeneration of the pyramidal tracts is rather marked, these being thereby sharply demarcated from the other parts of the section, there is also evidence of degeneration, which is older than that seen in the pyramidal tract, in those areas occupied by the spinocerebellar tracts A rather slight degree of stippling is seen throughout the remainder of the section occupied by the white matter *Sections through*

the brain stem at the level of the corpora quadrigemina inferior There is a rather extensive degeneration in the formatio reticularis and a somewhat milder grade of degeneration in the lateral and medial fillets, where there is a good deal of pigment accumulated in the perivascular spaces The pyramidal tracts show a like degree of disintegration, with typical beadlike formation of Marchi granules, where some of these fibers have been cut in a slightly longitudinal direction The small amount of stippling in the brachium pontis is probably pseudo-Marchi in character *Sections through the upper portion of the pons and medulla, at the level of the fifth nerve* Here a moderate degeneration is seen in the median fillet and in the pyramidal tract There is also some blackening of the fibers evident in the intramedullary portion of the fifth nerve as well as in those fibers which pass over the brachium conjunctivum, which may belong either to the lateral fillet or to Gowers' tract The remainder of the section is perfectly clear

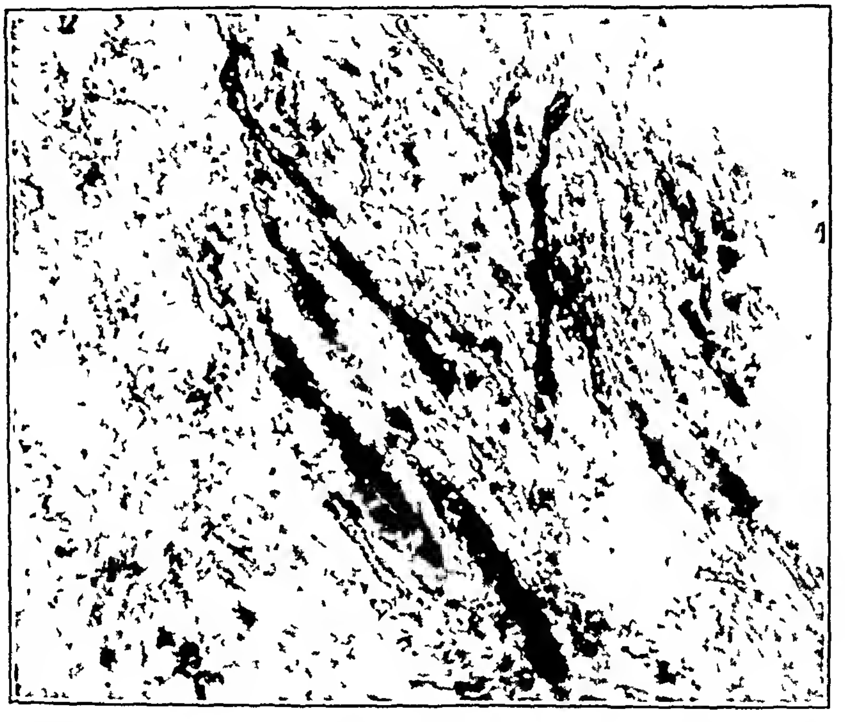

Fig 10 (Case 4)—Marchi stain ×100 Showing degeneration present in the corpus callosum Cross section of brain just posterior to optic chiasma

Bielchowsky Sections In the serial Bielchowsky sections are seen many blood vessels which are surrounded by areas lighter in color than the surrounding tissue, from which they are not sharply demarcated, in which the fibers appear to be disintegrated, axis cylinders, on passing through such an area, tend to become pale, somewhat granular and ultimately to disappear The neurofibrilli within the cells do not stain well, in general, though in those instances in which they can be seen, they look entirely normal

The neuroglia tissue, on the whole, as seen in the Weigert glia-fiber and in the Ramón y Cajal glia cell sections, appears to be normal, though there is possibly a diffuse increase in the glia cells and in the glia processes, some of which appear to be very massive and wavy, particularly in those sections prepared from the frontal lobe

In the sections stained with hematoxylin and eosin are found certain areas in the white matter which are of a pale, grayish-blue color, varying in size from 0 01 to 0 1 *mm* in diameter These areas look as though they might have been produced by some distention of the interfibrillar substance, there being no

particular change in the surrounding tissue As a rule the margin is fairly sharp In a good many instances this same cribriform appearance can be seen surrounding the perivascular spaces, which probably correspond to the areas of the same size seen in the preceding sections In a number of instances the nuclei of glia cells within these areas can be seen in various stages of degeneration, as shown in Figure 13 These changes are especially noted in the temporal gyri and about the calcarine fissures In the right putamen, near the ventricular wall, is seen a fairly recent hemorrhage about 1 mm in diameter

Thionin, toluidin blue and neutral red sections On the whole these sections present a fairly normal appearance The cyto architecture is undisturbed and the cells stain fairly well, although the Nissl bodies are not as distinct as one normally sees A few of the cells show a rather indistinct outline, which is often much distorted, and the dendrites are usually poorly defined Vacuoles of varying sizes can be observed, and the nuclei are often eccentric and in several instances partially extruded These changes occur to some extent

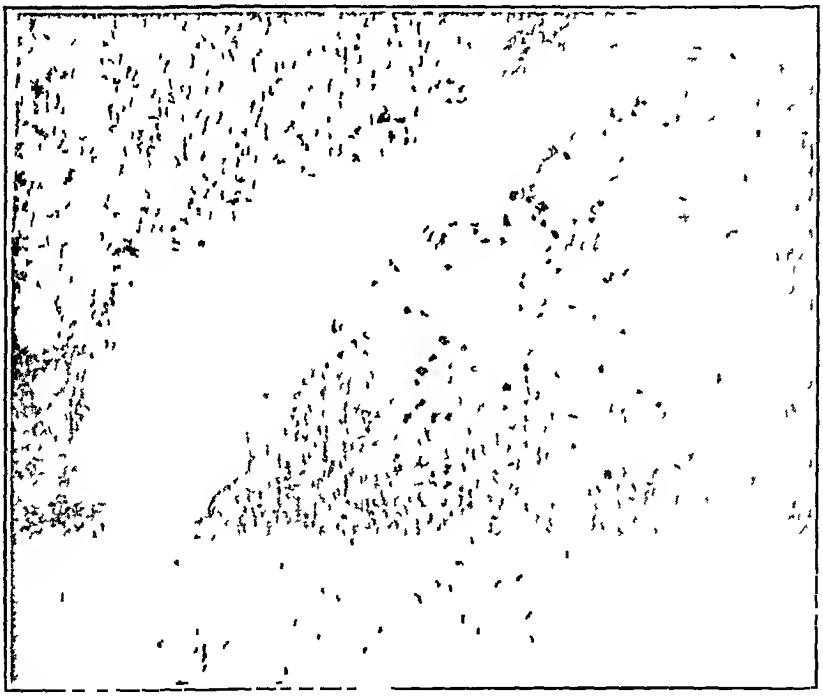

Fig 11 (Case 3) —Marchi stain × 100 Area of degeneration in proximity to blood vessel Compare with Figure 14

in all of the layers but are found most marked in the deep and superficial large pyramidal cells Typical axonal reaction was found in two or three instances in sections from the right Rolandic area All of these changes, with the exception of the axonal reaction, were found particularly marked in the frontal, Rolandic, and temporal lobes In sections from the calcerine area one also finds a slight degree of perivascular, small, round cell infiltration The cerebellum and basal nuclei showed no changes of interest

In the fuchsin-lichtgruen sections, 3 microns in thickness, prepared according to Alzheimer's instructions, most of the cells appear practically normal, though a good many contain, scattered throughout the cell, small, brilliant-red, fuchsinophilic granules, which vary in number from two or three to twenty or more granules to a cell One cell was found completely filled with such granules This stain also shows very beautifully the granules which are stained black by the osmic acid of Flemming's solution, some of them being very small, others very large, evidently formed by the coalition of the smaller granules

The blood vessels at the base show a moderate hypertrophy, principally of the media, though the intima also shows a slight thickening This hypertrophy is concentric and uniform throughout the periphery of the vessel The elastic tissue is normal in amount

CASE 2—(Necropsy 759) *History*—Mr A R S, 42 years of age, engaged in railroad construction, doing very hard work and being very much exposed, presented himself for examination May 19, 1908 He was married, had four children, three of which were living and well and one of which died of spina bifida His father died at 77 years of age of an unknown cause and the mother at 65 of "cold" Two brothers died from excessive use of liquor, and one brother, a twin with the patient, died when he was 1 week old There are three brothers living and well During the first six months of his life the

Fig 12 (Case 2)—Marchi stain ×50 Showing an area of perivascular degeneration and accumulation of "Abbauzellen"

patient was weakly, but after that grew well and strong Had measles, scarlet fever, and diphtheria in childhood but was never seriously ill He had a Neisserian infection about fifteen years and again eight years prior to examination, from which he recovered Denied having ever had syphilis For ten years the patient was a very heavy drinker, but said he had taken nothing during the previous six years In June, 1905, he was struck on the head by a bar which left no contusion or lump, though he regularly after that noted an occasional sharp pain in the top of his head Some four months later the scalp broke and there was a discharge of a little pus, two weeks later the diseased area was cut out and in a short time his scalp was wholly well He had no other injuries of consequence About the same time the patient noticed that he wanted more clothing for sleep than formerly At that time he had completed a hard three

days' tramp in the rain, going almost wholly without food He said that he had never been well since He also noticed that he became more easily irritated than before During all this time he noticed no anemia Since then his health had varied somewhat and at times he would feel entirely well, and then, for a few days would have a vague sense of being unwell In November, 1906, he noticed a beginning numbness in his fingers and in his toes, and in two weeks this sensation spread through the arms and legs to the body, where it had been present more or less ever since He also noticed trouble in walking, which bothered him a good deal for three months Always slept well until this time, but since then he had been bothered somewhat with insomnia About this time he began to be very pale and suffered some from shortness of breath He began taking cold water baths and massage and gained in weight from 185 to 210 pounds, but caught cold, after which he felt very sore for two or three days and lost all the weight he had gained In March, 1908, he visited

Fig 13 (Case 3)—Hematoxylin and eosin ×200 One of the sievelike areas occurring in the medullary substance This one was located near the sensory-motor area and contained a more or less necrotic center

the Mayo Clinic, where his case was diagnosed as pernicious anemia For nearly a month he improved very much but again caught cold and lost all previous gain Since then he had also had much pain in the base of his head and more recently between the shoulders and in the hands and arms There was also some numb feeling in the legs There were no shooting pains in the legs or cramps in the abdomen The bowel and bladder control was normal at the time of examination

Examination—On examination the patient appeared to be extremely anemic and the skin had a lemon yellow hue His weight was 180 pounds There was a double inguinal hernia The patient walked with the greatest difficulty and it was not possible for him to stand with his feet close together The pupillary reactions were normal The tongue was distinctly tremulous, moderately coated and projected straight When first seen there was a marked increase in the patellar and Achilles tendon reflexes and objective tests revealed a little sensory disturbance There was an ankle clonus on both sides and a double Bab-

inski phenomenon Subsequently, though his anemia was growing steadily worse, his reflexes gradually approached normal, finally became diminished, and ultimately disappeared There was some diminution of touch and pain sensibility in the hands and in the feet, and a very marked loss of joint sensibility in both the hands and the feet Toward the end he developed marked mental symptoms which began with some degree of mental sluggishness, and just preceding death developed into a distinct delirium ' His blood, examined on March 30, 1908, showed hemoglobin 47 per cent , red count 1,700,000, color index 1 3 +, 3,000 leukocytes, a few myelocytes, and some anisocytosis April 6 the hemoglobin was 47 per cent , April 11, 35 per cent , May 4, 57 per cent, and May 11, 53 per cent

Necropsy.—The patient died Sept 8, 1908, necropsy being performed twenty-one and a half hours after death The notes showed the following The patient was a well developed person, with fair general nutrition The body had

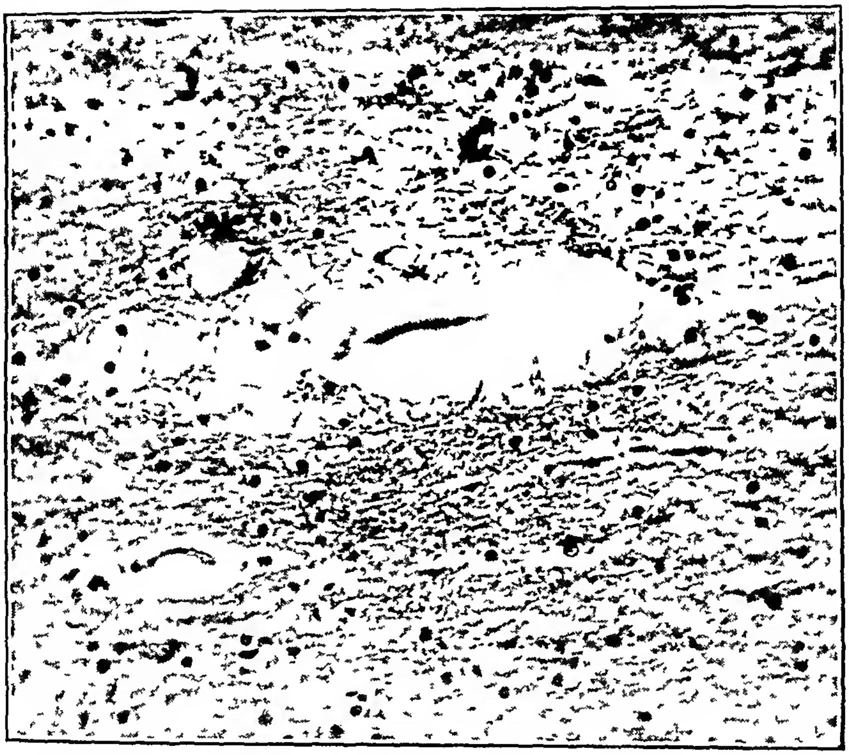

Fig 14 (Case 5) —Hematoxylin and eosin × 200 Section cutting through the left calcarine fissure, showing one of the numerous sievelike areas, in this instance surrounding a blood vessel

been injected with formaldehyd solution and contained scarcely any blood, all cavities being filled with this artificial fluid There was well marked lividity The heart was moderately enlarged and revealed a chronic valvular endocarditis of the aortic, bicuspid, and tricuspid valves Both left and right sides of the heart contained large chicken-fat clots There was a moderate thickening of the intima of the aorta The spleen weighed 282 gm and showed, microscopically, a hyaline thickening of the blood vessels The kidneys appeared to be normal at necropsy, though microscopically they showed an occasional sclerosed glomerulus The lungs showed some thickening of the pleura and the alveoli contained a good deal of serum in the dependent portions of the lung and an occasional polymorphonuclear leukocyte The adrenal was the seat of a new growth, possibly a hypernephroma The bone marrow was lemon yellow in color The liver and the gastro-intestinal tract were normal The pancreas showed a slight fatty change The pituitary gland was somewhat congested and showed a slight increase in connective tissue

Brain—The dura was normal in appearance, the sinuses were practically empty, and there was no evidence of pacchymeningitis The brain was pale and gray-white in color There was a marked edema of the pia-arachnoid, but no opacity The contour of the brain and of the convolutions was normal in appearance The ventricles were of normal size and the ventricular walls were smooth and glistening Fixation was good The blood vessels at the base showed no evidence of arteriosclerosis, the walls being very thin and tender The spinal cord showed a marked combined sclerosis of the type seen in pernicious anemia

Weigert Sections *Frontal sections* There is a certain amount of perivascular degeneration present In the medullary portion of the gyri, just under the gray layer, are found several small, circular, fairly sharply demarcated areas 0 1 to 0 2 mm in diameter There are about nine of these to the low power field A few are also noted in the gray layer *Sections posterior to*

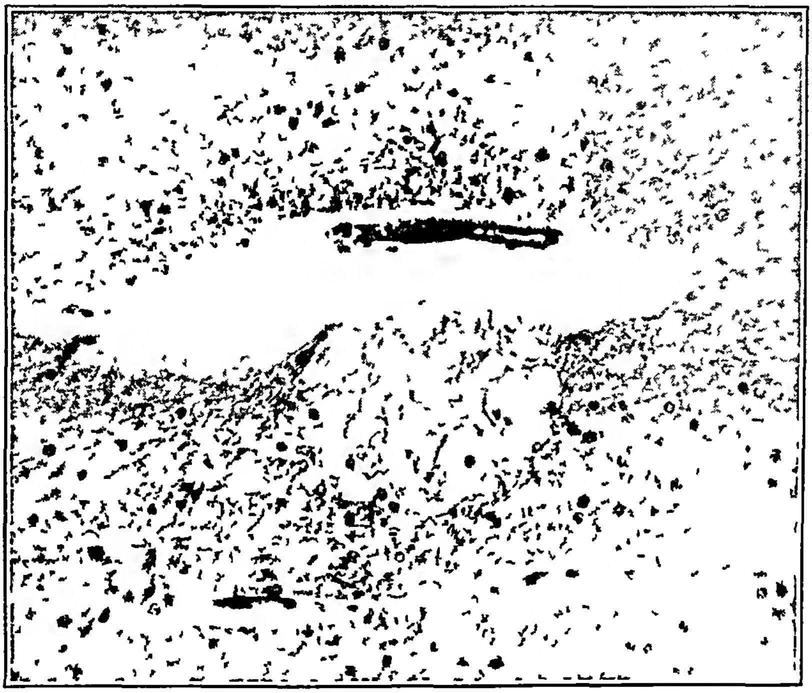

Fig 15 (Case 5) —Hematoxylin and eosin × 200 Same area as above figure The substance filling the gland-like structure at the side of the vessel is seen to be filled with a hyalin-like material, basophilic in reaction, and resembling in all respects the material present in the perivascular space, from which it appears to have been crowded into the tissue Compare with Figure 10

optic chiasma There is a very definite area of perivascular degeneration 0 2 by 0 4 mm in size in the centrum semiovale, also one in the corpus callosum The blood vessels appear to be normal *Sections through the middle of the crus* Some fifteen to twenty typical Lichtheim placques are noted in each centrum semiovale, also a number in the corpus callosum These are about 2 by 3 mm in size, and are usually associated with the blood vessels In one instance a capillary is seen to be perfectly normal in appearance to its point of bifurcation, where a large degenerated area is found, the entire structure resembling a palm tree, as shown in Figure 3 In the gray matter of the gyri one finds a few of the pale globular areas described in the preceding case *Sections through the occipital lobes* There is considerable perivascular degeneration present in many places throughout the white matter The sharply outlined circular areas, described as occurring in the medullary portions of the gyri, are found

here also *Sections through the pons* In the right brachium conjunctivum a perivascular area of degeneration can be seen *Sections through the olives and the dentate nucleus* Perfectly typical Lichtheim foci of small size, with disappearance and ballooning of the myelin sheaths, are seen in both corpora restiformes and in the pyramidal tracts In all other respects, these sections are normal in appearance

Marchi Sections *Frontal sections* The small, circular, white areas seen in the Weigert sections just below the gray layer can be seen here as relatively pale areas There is a very slight and diffuse stippling throughout the section, which is more marked in the fibers of the corpus callosum than elsewhere, the major part of this, however, is probably pseudo-Marchi in character *Sections through the optic chiasma* These sections are practically normal in appearance except for a slight deposit of granules in the perivascular spaces in the gray matter *Sections 0 5 cm posterior to the chiasma* There is a definite though moderate degeneration in the fibers of the corpus callosum, the optic

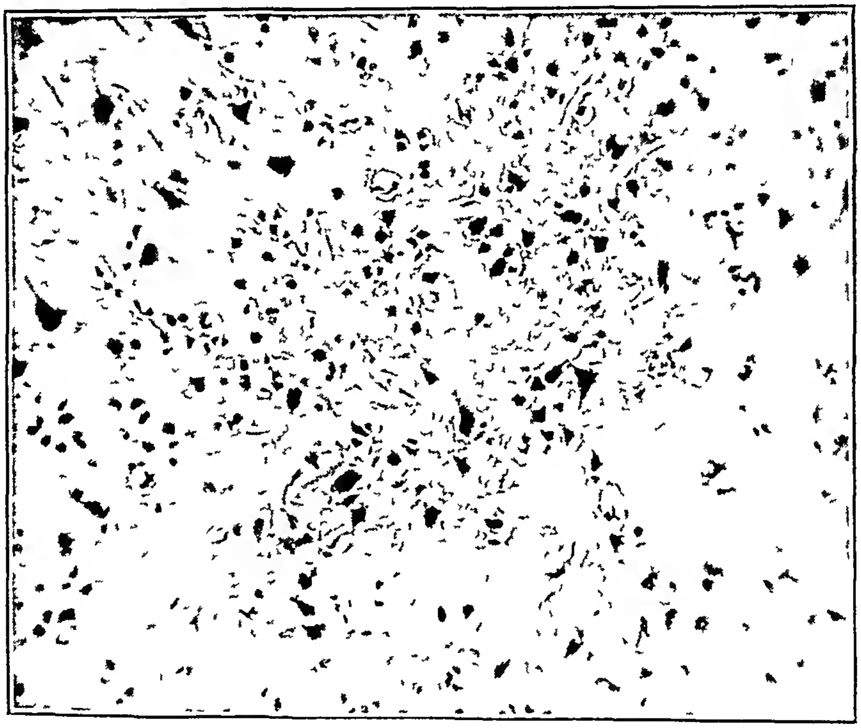

Fig 16 (Case 3) —Hematoxylin and eosin ×200 Left pre-Rolandic gyrus Three areas of pericellular destruction are noted, the lower right hand one being reproduced at a higher magnification in the following figure

tract is also moderately degenerated and shows the perivascular space of one of its blood vessels filled with an accumulation of pigment *Sections through crus* A slight stippling is noted throughout the section, which is uniform and which may not exceed that seen in a normal case There is, however, a very distinct, though rather slight degeneration of the fibers in the optic radiations The blood vessels throughout the section show a slight deposit of pigment in the perivascular spaces Surrounding some of the blood vessels, both in the gray and in the medullary portions, is a pale halo This is probably the counterpart of the light perivascular areas seen in the Weigert sections *Sections through occipital lobes* The degeneration in this portion of the brain is more definite than that seen further forward A number of blackened areas can be seen occurring about some of the capillaries of the medullary substance which are composed of degenerated nerve fibers and "Abbauzellen" *Sections through the pons and the overlying cerebellum, cutting through the dentate nucleus* There is a striking degeneration in both corpora restiformes, which is more pro-

nounced on one side than on the other, in which there appears a marked ballooning of the fibers, together with an extensive deposit of Marchi granules There is also a definite, though less intense, degeneration in the fibers of the pyramidal tract, together with a slight, diffuse degeneration of the remaining portion of the medullary substance In the vicinity of the dentate nucleus, particularly among the descending fibers one also sees some degenerating fibers *Sections through the pons, at the level of the decussation of the fourth nerve* There is a somewhat diffuse degeneration of moderate intensity in the fibers of the pyramidal tracts, in the median and lateral lemnisci, in the substantia reticularis, and in the decussating fiber of the fourth nerve The blood vessels in these areas show a moderate amount of perivascular deposit A smaller and somewhat thinner section taken through the temporal lobe shows probably some increase in the pigment of the cells, some of them, particularly those in the third temporal convolution, being almost a solid black The majority of cells, however, do not contain any excess pigment The degeneration of the short com-

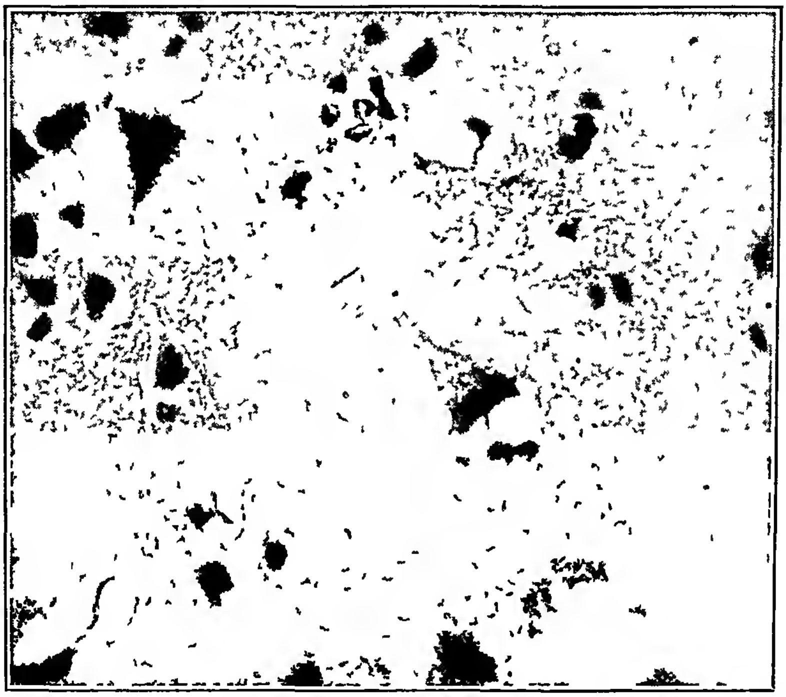

Fig 17—× 500 Showing in greater detail the pericellular area of tissue change The pyramidal cell itself is practically normal in appearance Two satellite cells are seen

missural fibers is apparently just as marked as is that of the longer fibers, and in the case of the third temporal convolution, there appears to be no more degeneration of the fibers than is seen elsewhere in the section A longitudinal section of the internal capsule shows a slight, rather diffuse degeneration of these fibers, the blood vessels show only very slight perivascular deposits

Bielchowsky Sections In the Bielchowsky slides one sees rather poorly defined elongated areas, which are paler than the surrounding tissue and which are usually, though not invariably, associated with blood vessels, as becomes evident from a study of the serial sections These areas are formed by a rather pale staining, somewhat granular, flocculent material, the approaching axis cylinders are seen to become pale, wavy, granular, and finally disintegrated A number of apparently normal fibers can usually be seen passing through these areas Sections taken from the thalamus are normal, except for the presence of a perivascular area similar to those just described

The glia fibers and glia cells of this brain are perfectly normal in appearance In sections stained with hematoxylin and eosin, one sees a number of pale areas, of uncertain definition, in which the fibrillar structure is seen grouped in somewhat coarse, wavy bundles These areas are particularly numerous in the Rolandic and occipital areas of the brain, and probably correspond to the lighter areas seen in preceding sections Some of these show a rather diffuse increase in glia cell nuclei Sections stained with thionin and toluidin blue show the pyramidal cells to be practically normal in appearance, save for a slight tigrolysis and occasional eccentricity of the nuclei In the right Rolandic area one sees a moderate amount of satellitosis Two instances of axonal degeneration were found in sections selected from the left precentral gyrus In the right first temporal gyrus is seen a blood vessel filled with polymorphonuclear cells The cerebellum appears to be perfectly normal In some of the overstained sections there are seen in the marginal gray layer, pale, more or less circular areas, these

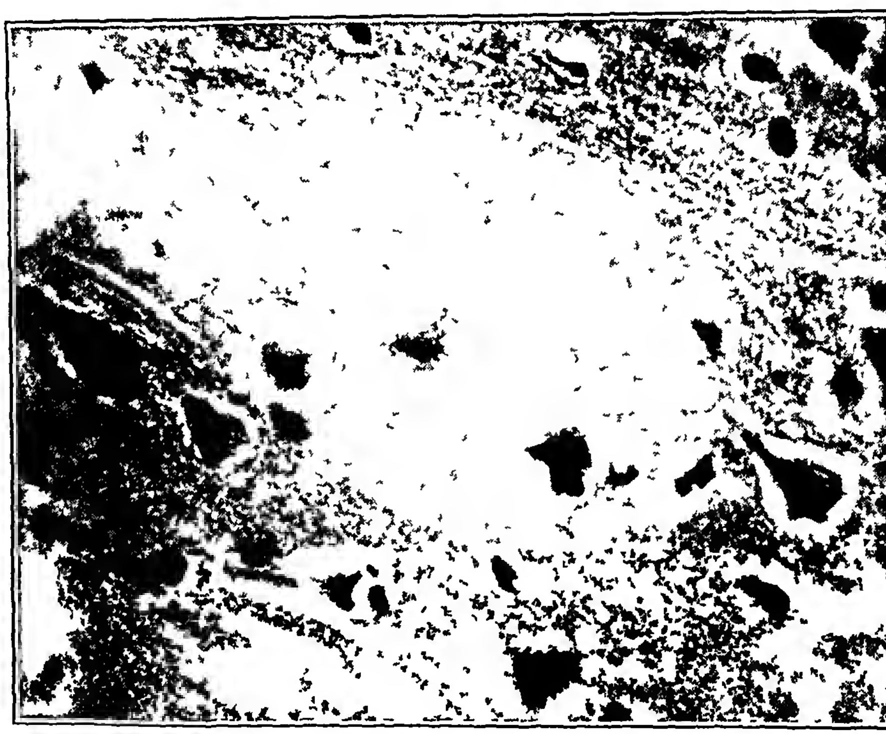

Fig 18 (Case 3) —Hematoxylin and eosin × 500 Pre-Rolandic gyrus, superficial large pyramidal cell layer Two pyramids are shown, in different degrees of degeneration, the lower one being only moderately involved, while the upper one shows a more marked destruction A neuronophage is seen in the lower cell also

not infrequently have in their center a nerve cell which shows sometimes slight, at other times very marked, evidences of degeneration Only one such area containing a cell was found in the *lichtgruenfuchsin* preparations, the cell being perfectly normal in appearance Four or five similar areas were found, though no cell could be seen in their center No fuchsinophilic granules could be found, all the cells being apparently normal

Case 3—(Necropsy 767) *History*—G W S, aged 40, married and a housewife, presented herself for examination May 20, 1908 The father died at the age of 78 and the mother of some intestinal trouble, which may have been tuberculosis There were three sisters living, one of whom had diabetes There is some neurotic tendency in the family, and the patient herself had been nervous for the previous three or four years, and the previous winter began exercising She incidentally took cold and subsequently there developed a sen-

sation of needles being pricked into her back and also a sensation in the foot as though the arch were falling There later developed a feeling of weakness and numbness in the legs, which in the course of time reached her knees, thighs, and back The patient gradually grew very much weaker and finally died, a diagnosis of pernicious anemia having been made Unfortunately there was no full record of her examination at hand, it was known, however, that the patient showed a very marked increase in her patellar reflexes

Necropsy—A necropsy was performed Sept 20, 1908, the record of which follows The body is that of an adult, well developed, but considerably emaciated female Rigor mortis is well marked and there is slight lividity The sacrum is a site of a moderate sized bedsore The abdominal, pleural and pericardial cavities contain no fluid The lungs are normal in appearance except for a few small areas of anthracosis and a number of peribronchial lymph nodes The heart is normal in size, rather flabby and shows no evidence of endo-

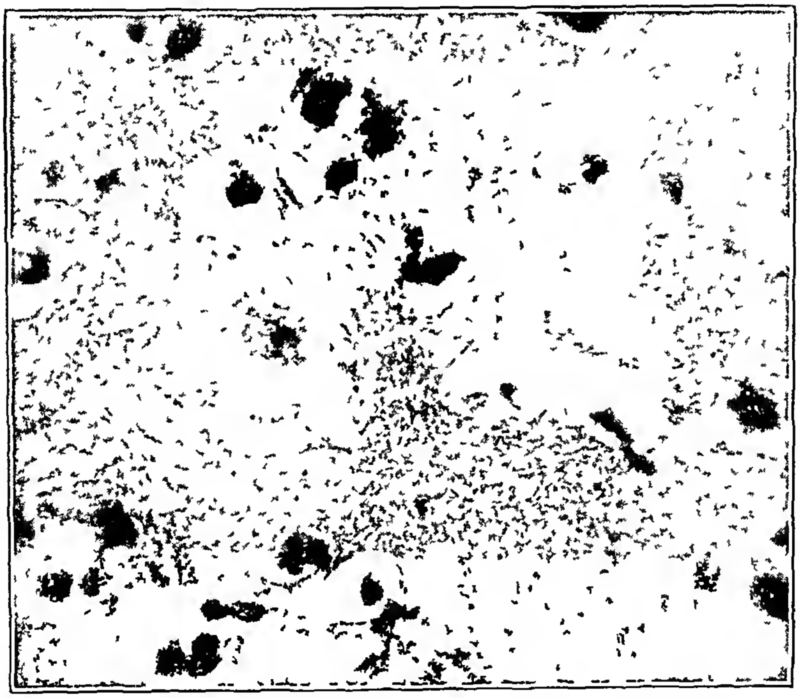

Fig 19 (Case 3)—Hematoxylin and eosin $\times 500$ Two pyramidal cells of the left superior temporal gyrus, surrounded by a zone of pallor, undergoing disintegration, only a trace of the pyramid to the right remaining

carditis The spleen is moderately increased in size and cuts with increased resistance In the kidneys of both sides are a very few small infarcts, the pyramids are distinctly congested, and the capsules, though somewhat thickened, strip readily Microscopically are seen a few areas of hemorrhage and an occasional sclerosed glomerulus, scattered throughout the section are many foci of lymphoid cells The liver shows some cellular infiltration of the border connective tissue, but is otherwise normal in appearance The spleen is practically normal save for some congestion and a hyalin thickening of the vessel walls There are some adhesions between the right ovary and the intestine The adrenals, pancreas and gastro-intestinal tracts present no pathologic changes Cultures from the heart blood, spleen and liver showed a growth of *Staphylococcus pyogenes aureus* in all

Brain—The scalp and the skull are normal The dura is free, practically normal in appearance, and the sinuses almost empty The brain is of a very pale, grayish-white color The vessels at the base are perhaps a trifle thickened

and stand open, but there is no atheroma present and they feel soft The choroidal vessels are normal in appearance The pia arachnoid shows considerable edema and is slightly opaque The convolutions are perhaps a trifle shrunken and the sulci a little deep over the convexity The ventricular walls are smooth and glistening There is possibly some dilatation of both ventricles, the left being a litle more dilated than the right The spinal cord shows a very marked subacute combined sclerosis, such as is seen typically in cases of pernicious anemia

Weigert Sections *Frontal area* Two or three small but characteristic areas of degeneration, such as are found in the spinal cord, are seen in this section, which are unassociated with blood vessels Surrounding a blood vessel, which was cut longitudinally, is seen an area of disintegration of the myelin, which is present in only a limited portion of its course, the rest of the surrounding tissue being normal in appearance, as shown in Figure 4 In the medullary substance, under the cortical layer of gray matter, are seen a number of more

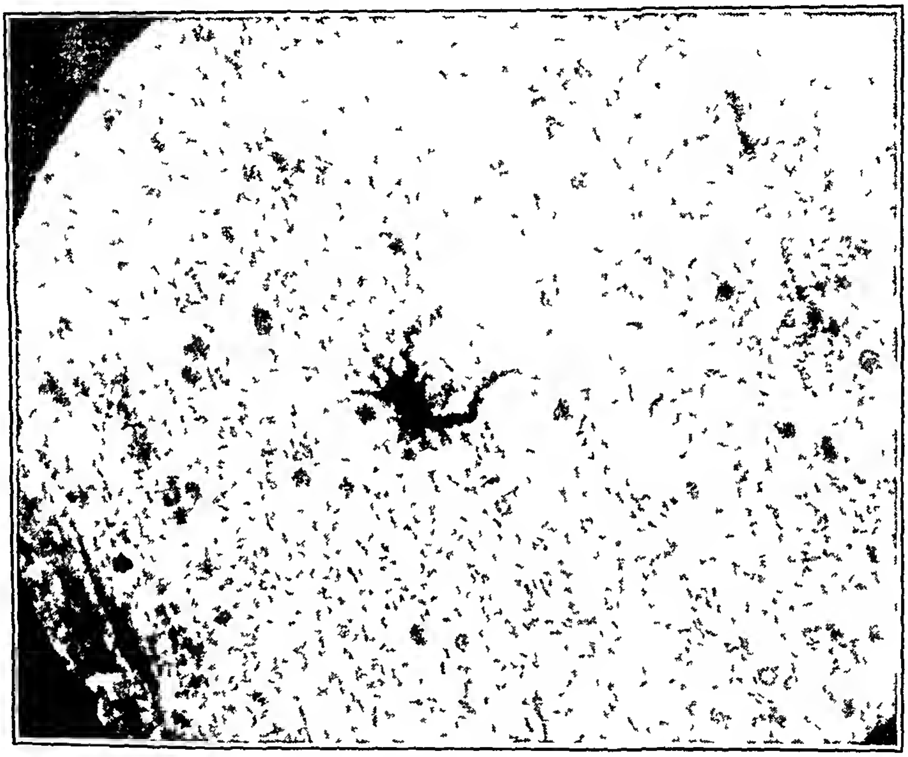

Fig 20 (Case 1) —Ramon y Cajal's gold stain for glia cells $\times$ 500 Illustrating the massive and wavy glia cell processes noted in some of the brains

or less circular areas of degeneration about 2 mm in diameter, similar to those described in the preceding case In certain locations they appear to push aside somewhat the radii passing into the gray matter *Sections passing through the posterior portion of the optic chiasma* The right temporal lobe, the island of Reil, and to a less extent the internal and external capsules, are rather pale and uniformly gray in color In this area there is seen a marked increase in the number of small blood vessels, all of them being 1 mm or less in diameter The inferior temporal gyrus on this side is in part definitely softened, with cavity formation The perivascular spaces are seen to be enlarged and filled with a granular debris The temporal lobe on the left shows a somewhat similar change, save that the softening is less advanced, and the myelin more deeply stained The blood vessels in this locality are present in somewhat increased numbers and are comparatively large, some of them up to 2 5 mm in diameter Many of these vessels are surrounded by diffuse areas of degeneration which are elongated in the course of the nerve fibers The other findings are very

much as in the preceding section *Sections through the middle of the crus* The same area of diffuse, partial softening is noted in the right temporal lobe and presents the same characteristics noted above This also holds true for the left side, though the blood vessels here are somewhat smaller Ballooning of the fibers can be seen in many of these areas The small circular areas, described as occurring in the medullary portion of the gyri, are seen here also *Occipital area* The diffuse area of degeneration on the left side is seen in this section to extend from the lateral wall of the ventricle toward the periphery, where there is a margin of apparently normal tissue There is some dilatation of the blood vessels in all portions of this section *Sections through the cerebellum* In several of the laminae of the cerebellum are seen one or more pale, fairly well defined circular areas which resemble those described in previous sections *Sections through the pons and the cerebellum* Except for the finding noted in the preceding section the tissue was apparently normal

Marchi Sections *Frontal area* Grossly there are seen in the superficial gray layer a number of light points which are usually circular, though sometimes elongated and branched, as though accompanying blood vessels Microscopically there appears some diffuse stippling which, however, is probably pseudo-Marchi in character No recent areas of degeneration can be detected Slight perivascular accumulations are present here and there The cells of the cortex contain about the normal amount of pigmentation *Sections through the chiasma* In the white matter are seen areas which are paler than the surrounding tissue, and which resemble in their general outline those seen in the Weigert sections These are present in considerable numbers, particularly in the centrum semiovale Microscopically, very marked degeneration is seen, which in places appears in the form of very small foci which probably represent the earlier stages of the Lichtheim plaques As a rule these are associated with blood vessels, though this is not always evident In these areas swollen fibers appear in great numbers and in all stages of transition from the blackened fibers to those completely disintegrated into fat droplets "Abbauzellen," which contain these droplets as very fine, dustlike particles, can be seen surrounding some of the capillaries in great numbers *Sections through the level of the crus* There is a moderate amount of rather diffuse disintegration in the substance of white matter, particularly in the fibers passing through the internal capsule and in the corpus callosum The pyramidal cells of the marginal gray are in places rather deeply pigmented, this is especially marked in the gyrus cinguli where in many instances the entire cell seems to be wholly filled with pigment globules varying greatly in size As far as the lighter areas of the gray matter are concerned these are also found, in very few numbers, however, in the basal ganglia, the island of Reil being more or less free from them *Occipital area* A rather marked degeneration is present throughout the medullary substance Blood vessels, which appear to be numerous and dilated, show a considerable amount of perivascular accumulation *Sections through the pons at the level of the corpora quadrigemina inferior* These sections are practically normal in appearance, save for a slight amount of perivascular deposit

Bielchowsky Sections In the Bielchowsky sections in the marginal gray layer are seen fairly numerous, pale, more or less circular areas with margins that are somewhat poorly defined The centers of these areas are traversed by fibers which become paler as they pass into them from the surrounding tissue, often being lost in the relatively structureless center The frequency with which pyramidal cells are seen to occupy the centers of these areas, forces the conclusion that they must in some manner be related to the so-called pericellular lymph space of Obersteiner Unfortunately the intracellular fibrilli failed to stain clearly in these sections, though the cells, in other respects, appear to be about normal Similar areas, though in lesser numbers, are also seen in the medullary substance, where they might be likened to localized patches of edema, giving the structure a more or less sievelike appearance

The glia fibers and cells appear in this brain to be perfectly normal and show little, if any, evidence of reaction even in the vicinity of the softened areas in the left temporal lobes

In section stained with hematoxylin and eosin, the pale foci described in the preceding sections of this case can be studied particularly well They are most numerous in the gray layer overlying the gyri, appearing in numbers as high as six to ten to the low power field of the microscope, and found to be most numerous in the convolutions of the temporal lobe They are seen, as a rule, to be more or less circular, then usually surrounding a pyramidal cell or somewhat elongated, in which case they generally follow the course of a vessel The cells themselves which are found within these areas, not infrequently show degenerative changes Somewhat larger patches, though similar in other respects, are found in the medullary substance of the gyri Within the right temporal lobe is found an area of softening with a cavity about 1 cm in diameter, surrounding which is a diffuse zone which shows evidence of mesodermal reaction There are also seen in this portion of the cortex numerous hemorrhages of small size The internal capsule and basal nuclei appear to be perfectly normal In the thionin and toluidin blue sections the foci which have been described as occurring in the marginal gray layer can be studied to the best advantage All stages of their formation, from their very incipiency, in which there appears a very narrow haze surrounding some of the pyramidal cells, to their fullest development, in which they appear as a broad halo surrounding the cells more or less concentrically, can be traced The cells themselves, in some instances, appear perfectly normal, in others there is seen a rather marked tigrolysis and eccentricity of the nucleus, and in still others is noted in addition, a varying degree of vacuolization One of these cells showed a very marked degree of tigrolysis, loss of cell processes, marked vacuolization, partial extrusion of a swollen, rather deeply stained and ill defined nucleus with a pale nucleolus enlarged about three times its normal size, and eight satellite cells, four of them neuronophages In another instance this area surrounded the base of one of the larger pyramidal cells which showed tigrolysis and a moderate degree of vacuolization These changes are most marked in the second pyramidal layer The size of the surrounding area and the degree of destruction of the cell seem to bear no definite relationship toward each other, however, those cells which show the highest degree of disintegration are usually surrounded by halos of considerable size A good many of them are found in which only the residue of a destroyed pyramidal cell can be seen This change is most marked in the temporal lobes, though the right and left frontal, the right and left Rolandic, and the right and left occipital gyri all show it to some degree In a section of the left calcarine area is found, in the layer of stellate cells, a circular, rather deeply staining, more or less coarsely granular area about 50 microns in diameter, which is in turn surrounded in about four fifths of its circumference by a very narrow reef of similar material The whole structure looks as though it might have been derived from disintegrated glia cell nuclei, and, although it does not correspond in all of its details to the foci described by Schroeder, it was the only lesion found in any of these brains which approached in appearance the plaques described by him Aside from these changes, which are very obvious, the majority of cells show little in addition to a certain amount of tigrolysis, some eccentricity of the nuclei, which in certain instances are more deeply stained than normal, and a fairly marked degree of satellitosis In a few instances there is complete disintegration of the cell All of these changes occur with greatest frequency in the second and third pyramidal cell layers The sievelike areas, described in preceding sections as occurring in the medullary portion, are found here also, but present no additional features In no instance does there appear to be any increase in the glia cell nuclei Near one of the capillaries in the left internal capsule there is found a clump of streptococci without evidences of surrounding tissue reaction

Cells which present a moderate number of fuchsinophilic granules are fairly numerous, though none found within the pale areas of the gray matter are seen to contain them

CASE 4—(Necropsy 142587)[2] H W L first visited the clinic Oct 4, 1915 He was 48 years of age, married, and a farmer His health in the past had been good, save for some chronic pain for twenty-five years in his knee which had a number of lumps on it About two years previously an operation had been done on the knee, from which two calcareous masses, the size of a flattened plum, were removed Soon after this he noticed that he was growing weak, that the color of his lips and nails was pale, and that his feet and hands became somewhat numb His appetite was also poor and he became gradually weaker, lost in weight and was generally run down, but was not compelled to go to bed July, 1914, he noticed that he would become dizzy on slight exertion and that his heart would palpitate easily At about this time he was operated on for some stomach distress, which resulted in a negative exploration After the operation he felt somewhat better and did some work in the fall of 1914 In December, however, he was compelled to go to bed where he remained for three months on account of weakness, after which he regained strength and was able to be up and about, off and on, until one month prior to his examination Since then he had been bedridden and suffered from profound weakness He also had some vague gastric distress but no hemorrhages, he had no appetite and, a month previously vomited every evening for a week Fowler's solution and Blaud's pills had been administered There were no genito-urinary complaints

Examination—The physical findings showed a marked pyorrhea There was extreme weakness, pallor, and much loss of weight which could not be accurately secured on account of his weakened condition The systolic blood pressure was 80, the diastolic 20, and the pulse 100 In the calf of his right leg there was a muscle stone the size of a flattened plum The blood examination on October 4 showed 18 per cent hemoglobin, 1,030,000 red cells, color index 0 8 +, and 4,600 leukocytes A differential count of 300 cells was made, which showed 47 3 per cent polymorphonuclears, 46 3 per cent small lymphocytes, 4 3 per cent large lymphocytes, 1 7 per cent eosinophils, 0 3 per cent basophils, 2 normoblasts, moderate anisocytosis, slight poikilocytosis, a moderate granular degeneration of the erythrocytes, and slight polychromatophilia The hemoglobin during October showed on the seventh, 28 per cent, the eighth, 27 per cent, the eleventh, 45 per cent, the thirteenth, 38 per cent October 6, one pint of blood was transfused November 4, the blood count was as follows 30 per cent hemoglobin, 2,000,000 red cells, 0 7 + color index, 8,600 leukocytes, with a differential count of 39 7 per cent polynuclear neutrophils, 53 per cent small lymphocytes, 5 7 per cent large lymphocytes, 1 3 per cent eosinophils, 0 3 per cent basophils, 36 normoblasts, moderate anisocytosis, slight poikilocytosis, and polychromatophilia The diagnosis of pernicious anemia was made October 15, a splenectomy was performed, at which time it was noted that gallstones were present, but these were not removed

The patient returned June 20, 1916 On leaving, in October, the patient returned to his home and spent most of the time in bed, being quite weak He was bothered a great deal with palpitation of the heart on little exertion His legs were very unsteady and sensation in his feet was diminishing

Neurologic Examination—A neurologic examination, made July 5, showed the right pupil to be larger than the left A watch was heard 4 inches from the ear on the left, and a normal distance of 30 inches on the right Touch, pain and temperature were slightly impaired over the face, as compared to the

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2 The clinical data and the pathologic material of the following case were obtained through the kindness of Drs Walter D Sheldon and Wayne W Bissell of the Mayo Clinic, Rochester, Minn

chest The muscles were uniformly weak Tactile sensation was very much diminished in the fingers and moderately diminished below the wrist, gradually increasing to normal above the mid forearm It was almost completely absent in the feet, was moderately impaired above the ankles and increased gradually to normal, 6 inches above the knees Pain sensibility was moderately impaired in the hands, increasing to normal as in touch In the toes it was almost completely absent, increasing gradually to normal above the knees Temperature sensation was moderately impaired in the hands, increasing to normal as in touch, and somewhat more impaired in the feet, increasing as above Vibration sensation, tested with a tuning fork of 256 v, was absent over all bony prominences below the third lumbar spine Joint sensibility was normal in the fingers and slightly impaired in the toes Muscle pain sense was normal The biceps, triceps and supinator reflexes were very active The upper, middle and lower abdominal reflexes were normal on the right and moderately impaired on the left The patellar tendon reflexes were normal, as was the left Achilles tendon reflex, the right being obtained only on reinforcement There was a rather marked Romberg The gait was slow and weak Speech was slow, but otherwise normal Coordination was normal in the finger-nose test and perhaps slightly impaired in the heel-knee-toe test There was no tremor A diagnosis of subacute combined sclerosis was made The patient was transfused three times, first on June 25, when 500 c c of blood were transfused by the sodium citrate method, then, July 17, when the same amount was transfused, and again on August 9, when 600 c c were transfused An examination of the duodenal contents showed the same to be dark yellow in color and gave the following values, estimated by the Schneider method Bilirubin + + +, urobilinogen (3 4 × 200) 700, urobilin (5 × 200) 1,000, making a total of 1,700 units

Aug 22, 1916 A full neurologic examination at this time was impossible on account of the patient's weakened condition When seen he had jerking movements of the right arm which came on every few minutes Relatives said that this was also present in the left arm and both legs and even in the head and body There was subjective numbness in the arms to the elbows, and in the body below the belt The right pupil was larger than the left, and immobile to light, which may possibly be accounted for in part by the morphin which was required to allay the acute excitement from which he at times suffered Pin pricks were felt in the fingers and in the toes, further than this sensation could not be tested There was no definite paralysis anywhere, though the general weakness was extreme Reflexes in the arms were moderately increased, the knee jerks were active, the Achilles tendon reflexes were very active The plantar response was uncertain There was a marked fluctuation in attention

Necropsy—The patient died Aug 25, 1916 The following findings in the order of their importance, were abstracted from the necropsy report

There is a very marked general anemia with marked pallor of the tissues of the body, of the brain, and of the spinal cord A marked hyperplasia of the red bone marrow in the ribs and in the bodies of the vertebrae is noted There are marked fatty changes present in the myocardium, producing the so-called "thrush breast" heart, in the pancreas, kidneys and liver The spleen is absent, but a small accessory spleen is found The proximal end of the splenic vein and the distal end of the splenic artery are occluded by scar tissue Healed atrophic scars are present in the midline and in the left rectus region Fibrous adhesions are found between the great omentum and the peritoneum, adjacent to the left rectus laparotomy wound, and between the transverse colon and the midline laparotomy scars There is a moderate nodular fatty change in the lining of the aorta and in the aortic and mitral valvular leaflets The distribution of the yellow material of the adrenal cortices is uneven A slight hypostatic bronchopneumonia of the dependent portion of the right lung and a moderate bilateral hypostatic edema and hyperemia of both lungs are present, and slight

petechial hemorrhages are found in the visceral pleura of the dependent portions of both lungs There is a marked hyperemia and a hyperplasia of the mesenteric, retroperitoneal, biliary, lateral lumbar, and iliac lymph nodes A white stellate scar in the mesentery of the small bowel is noted The costal cartilages show a partial ossification The mastoid and petrous temporal bones are unusually cellular There is an absence of two toes on the left foot and an atrophic scar is present over the right knee The head is partly bald and the teeth are absent A large persistent membraneous Eustachian valve is seen The prepuce is redundant and there is a slight phimosis Sections from the liver for histologic examination show a slight congestion, marked fatty degeneration, and small areas of focal necrosis The heart shows very marked fatty changes The pancreas is normal The adrenals show a moderate amount of fat The lungs show a bronchial pneumonia There is a chronic interstitial nephritis and the kidney tissues are infiltrated with leukocytes Muscle tissue from the chest wall is negative The weight of the spleen is 558 gm and there is a slight chronic splenitis with cellular degeneration and a perisplenitis

Weigert sections of the spinal cord are practically normal in appearance, with the exception of possibly a little thinning out of the fibers in the posterior columns in the upper thoracic portion The Marchi sections of the spinal cord show a very extensive and comparatively recent combined sclerosis, such as is found in cases of pernicious anemia, the degeneration being most marked in the lower cervical and in the upper thoracic segments

Brain—The dura is normal in appearance, though very pale, and the sinuses are empty The brain is almost a pearly white, the size and the contour of the gyri being normal in appearance The leptomeninges show a moderate amount of edema and are very slightly clouded The ventricles appear to be normal The arteries at the base show a very slight degree of thickening but no atheromatous changes

Weigert Sections *Frontal sections* Five or ten foci, of the type found in the spinal cord, are seen in the medullary substance of these sections, some of them being related to blood vessels while others were not, so far as could be determined *Sections cutting through the brain just posterior to the chiasma* With the unaided eye one can see a half dozen or more areas of pallor, ranging in size from 1 5 mm to 3 or 4 mm in diameter The largest of these are seen in the white matter of the third frontal convolution on the right side, another, 3 mm in diameter, is seen located near the middle of the corpus callosum and still two others of about the same size in the temporal lobe on the left A distinctly pale area, somewhat triangular in shape, and about 2 5 mm in diameter, is seen at the juncture of the inner and outer portions of the right globus pallidus, just above the anterior commissure Under the microscope, these foci appear in large numbers and vary considerably in size and shape, most of them being independent of blood vessels The area in the globus pallidus is seen to be caused by a destruction of the medullated fibers passing through that portion and a paling of the surrounding gray matter *Sections through the crus* Twenty or thirty such areas can be seen with the unaided eye, located in the white matter These resemble the plaques described above, save that they are more numerous, though somewhat smaller Marked ballooning of the fibers is noted The plaques themselves present very irregular margins and are elongated in the direction of the fibers, some of them give evidence of having become enlarged by fusion of two or three separate areas *Sections through the occipital lobes* Some fifteen to twenty of these plaques can be seen grossly These are distributed more or less uniformly throughout the white matter, though the fourchette contains relatively more of them Sections through the middle of the pons are perfectly normal in appearance

Marchi Sections *Sections through frontal lobes at the level of the genu of the corpus callosum* There is a diffuse degeneration of moderate intensity throughout the section, with a corresponding degree of perivascular accumulation A few foci appear in which the degeneration is particularly marked The

corpus callosum shows no more degeneration than is seen in other parts of the section. The cortical cells of the gray matter contain the normal amount of pigment. *Sections through the chiasma.* This section shows the same changes as the one just described, the fibers of the internal capsule sharing in the degeneration. *Sections passing through the brain 1.5 cm. posterior to chiasma.* There is a very extensive degeneration, rather general in its distribution, throughout the medullary portion of the section. This degeneration becomes somewhat more marked in the vicinity of the corpus callosum and of the pyramidal tracts, where the fibers appear swollen and sometimes resemble chains of beads. In the centrum semiovale, both right and left, a number of very small deposits of blackened granules are found, which presumably represent early stages of disintegration corresponding to the Lichtheim foci. There is also some perivascular deposit present. In general, the cells of the marginal gray, as well as those of the basal nuclei, appear to be normal. *Sections through the crus.* Grossly, one can see a number of lighter foci in the medullary substance, which probably correspond to some of the areas seen in the Weigert sections. There is a diffuse and very well marked degeneration present which seems to be almost as intense in the short association fibers going from one gyrus to another as it is in the longer commissural tracts, the degeneration being little more marked in the corpus callosum and the crus than elsewhere. While some of the cortical cells appear excessively pigmented, the average amount of pigment probably does not exceed the normal. *Occipital sections.* With the unaided eye the same pale areas appear in these sections as already noted, which microscopically, at times, show a pigment deposit at their peripheries. As in the preceding section, so here, we find a well marked and diffuse degeneration of the white fibers; this is particularly intense in the fibers of the splenium and of the optic radiations. Perivascular accumulations are commensurate with the degree of degeneration noted. In the cells of the gray layer, overlying some of the superior convolutions, one can note a considerable amount of pigment; the degeneration of the white fibers springing from this portion of the cortex is, however, not more marked than that occurring in the fibers located in the medullary rays of other convolutions. *Sections through the cerebellum.* There is a moderate degree of degeneration in practically all of the cerebellar laminae, with a corresponding deposit of detritus in the perivascular spaces. There appears to be no abnormal pigmentation in any of the Purkinje cells. *Sections through the pons at the level of the decussation of the fourth nerves.* There is a very definite and rather marked degeneration in the fibers of the median lemniscus, as well as a rather moderate amount of degeneration in the decussating fibers of the fourth nerve. A slight degree of degeneration is also observed in the reticular formation, in the fibers of the posterior longitudinal bundle, and in the pyramidal tracts; in these structures, however, the degeneration is very slight in degree and of questionable significance. Other structures appear to be practically normal. *Sections through the cord immediately below the pons.* There is a definite, though slight, degeneration present in the location occupied by the spinocerebellar tracts, particularly on one side. The remainder of the section, though showing a slight stippling, is probably negative. *Sections through the olives.* A fairly well marked degeneration is noted in the location occupied by the spinocerebellar tracts and a somewhat less marked but more recent change in the fibers of the median raphe. The fibers of the pyramidal tracts show a still less, though quite definite, degeneration.

Bielschowsky Sections. In the Bielschowsky sections a number of foci, about 0.3 mm. in diameter, are found which are oval, the long axis lying in the direction of the fibers. These show in their centers a marked thinning out of the axis cylinders, so that only a few of them are seen here, compared to the number seen in the surrounding tissue. In the thalamus a very similar area is noted. The cells appear to be normal and the neurofibril stain fairly satisfactory. As seen in the Ramon y Cajal gold sections, the glia fibers appear to be more massive, wavy, knotted and irregular in contour than is noted in any of the

control sections The hematoxylin and eosin sections show a number of foci in the white matter which resemble localized patches of edema, in that the fibrillar structure is here somewhat crowded aside and the interfibrillar meshes enlarged In one case, the center is formed by a more or less structureless and apparently necrotic mass In all other respects the sections appear to be normal, and nowhere is an increase in glia cell nuclei apparent

In sections stained with thionin and toluidin blue, particularly those chosen from the right and left Rolandic areas, and somewhat less so in those from the temporal areas, are seen numerous areas which resemble the foci described in the hematoxylin and eosin sections, save that the change is carried still further, the entire structure resembling a gland The pyramidal cells, on the whole, are practically normal in appearance, save for a slight degree of vacuolization and some satellitosis A number of the cells show changes which are somewhat more marked, thus, in one cell there is a perinuclear tigrolysis, the nucleus being stained a deep blue and the nuclear membrane very indistinct This cell somewhat suggests the picture seen in axonal degenerations The Nissl bodies, however, are, in general, well preserved In the *Lichtgruenfuchsin* sections a few pyramidal cells are noted which contain a small number of fuchsinophilic granules, a number of others, however, are literally packed with large-sized, brilliant red granules The blood vessels are normal in appearance and the vessel walls uniformly thin

Case 5—(Necropsy 16-15) *History*—S O H, 51 years of age, Norwegian, single, was admitted to the hospital on the medical service Sept 24, 1914 He was born in Wisconsin where he lived for three years, and then came to Minnesota where he lived most of the time For twenty years he was a storekeeper in a small town, but the past year changed his occupation to that of selling postcards His average weight was 200 pounds, which in the last four years decreased to 150 pounds The father died at 60 of kidney trouble and the mother at 50, presumably of heart disease The patient had four brothers, two of whom were living and well, the other two were said to have had fits and died in the attacks when young men There were four sisters, one living and well and three dead from unknown causes The patient generally slept well and his appetite had been good until recently The bowels had been severely constipated most of the time He did not use tobacco and denied using drugs Up to three years previous to examination he used alcohol to excess, but the last few years took only an occasional glass of beer Eight years prior he contracted gonorrhea, which became chronic, discharging for at least two years As a boy he was always healthy, but when he grew up his stomach began bothering him off and on, the attacks of gastric distress coming on after drinking hard and lasting for about a week He had about two of these attacks, on the average, in a year He was otherwise well until the present trouble began About two years previously he began having rheumatic pains in the feet which gradually worked up the legs into the body He also had frequent attacks of gastric distress, which, however, were no longer associated with drinking His feet became numb and in the previous summer he noticed that he would frequently stumble at night or, if he turned quickly, would fall There was also a sensation of oppression around the abdomen which was accompanied by general pain and tenderness Although these symptoms have been gradually growing worse, the patient was able to continue working until September 23, the night before he entered the hospital

Physical Examination—A physical examination showed the patient to be fairly well nourished, but very pale and somewhat yellowish in color, with a slight puffiness under the eyes There was a marked pyorrhea, and most of the teeth were missing and replaced by plates A slight eczema marginatum was present on the penis and scrotum There was also some edema present in the legs Aside from this, physical examination was practically negative The blood pressure was 100 systolic and 72 diastolic A urine analysis, made

September 25, showed nothing abnormal, November 25 it was found to contain a trace of albumin and some leukocytes December 19 an analysis showed urobilinogen 3 + and urobilin 3 +, there were no amino-acids present Examinations of the stool December 18 and 28 revealed no ova or parasites A Wassermann test of the blood was negative The spinal fluid showed a Nonne-Appelt, Phase I negative, four small lymphocytes to the cubic millimeter and negative Wassermann The results of the blood examinations were as follows September 25, 80 per cent hemoglobin, 5,000 leukocytes, October 7, 80 per cent, hemoglobin, 8,200 leukocytes, 4,900,000 red cells, marked anisocytosis, marked poikilocytosis, and slight polychromatophilia, October 20, 75 per cent hemoglobin, 6,400 leukocytes, 4,700,000 red cells, November 7, 55 per cent hemoglobin, 6,700 leukocytes, 2,000,000 red cells, and a color index of 1 37, November 19, 50 per cent hemoglobin and a differential count of 74 per cent polynuclear neutrophils, 23 per cent small lymphocytes, 2 per cent mononuclears, 1 per cent eosinophils, November 30, 50 per cent hemoglobin, 5,700 leukocytes, 1,900,000 red cells, and a differential count of 74 per cent polynuclear neutrophils, 24 per cent lymphocytes, and 1 per cent eosinophils, December 7, 30 per cent hemoglobin, 3,500 leukocytes, 1,500,000 red cells, poikilocytosis, anisocytosis, and megaloblasts, December 20, 35 per cent hemoglobin, 3,000 leukocytes, January 2, 1915, 4,000 leukocytes, 1,400,000 red cells, February 5, 35 per cent hemoglobin, 4,100 leukocytes, 752,000 red cells

Neurologic Examination—The neurologic examination disclosed the following The nose was normal to inspection and the sense of smell, as tested with perfume, soap and other articles on his stand, normal The patient could read bold faced type of about 5 mm, but could not read finer print of 2 mm The field of vision was normal to a rough test There was no strabismus, exophthalmos or diplopia A slight horizontal nystagmus, which developed on looking toward the extreme right or left, coming on after a slight fatigue of the occular muscles, was noted The movements of the eyes were normal in all directions and convergence was good The pupils were circular, equal in size and moderately contracted, with a normal reaction to light and accommodation, both direct and consensual Sensation over the distribution of the fifth was normal for touch, pain, and pressure The corneal and conjunctival reflexes were normal Movements of the jaw, both horizontal and vertical, were normal in amplitude but somewhat deficient in power The patient could wrinkle his forehead, close his eyes, and move his lips normally, save that in showing his teeth the left angle of the mouth was retracted a little further than the right The ears were normal to inspection and hearing slightly impaired, the Weber, Rinne, and Schwabach tests were normal There was no tinnitus and the patient rarely had vertigo, which might come on when the patient attempted to sit up There was no difficulty in phonation, breathing or swallowing The palate moved normally and the palate and pharyngeal reflexes were present Pulse was normal in rate The sterno-mastoid and trapezius muscles were normal, save for a slight deficiency in power The tongue was protruded in the midline, showed no atrophy or fibrillation, but presented a slight general tremor, with slight impairment in power There was subjective prickling of the fingers and of the toes Sensation, as tested with cotton, appeared to be diminished on the palmar surface of the right hand below the level of the wrist and on the dorsum, below the middle of the second phalanges, of all fingers, and on the distal phalanx of the thumb On the left hand, cotton touch was about normal In the feet the sensibility to cotton touch was impaired on both sides below a point 4 inches above the external malleolus and 2 inches above the internal malleolus Pain sensibility was normal in both hands and feet, and both touch and pain sensibility were normal over the rest of the body Vibration sensation seemed to be impaired below the right wrist and was altogether absent over the head of the fifth metacarpal bone and digit It was slightly diminished on the left hand below the wrist, but was nowhere entirely absent There was complete pallanesthesia below the middle thoracic vertebra Muscle pain sense and sensitiveness of

the nerve trunks were normal The finger to finger and the finger to nose tests were fairly well performed, but there was a definite ataxia in both legs which became evident in the heel-knee-toe test The patient was at times unaware of the exact location of his legs in the bed Joint sense in the toes was completely absent, though the patient knew which toe had been touched There was a very marked Romberg There was general muscular weakness, and the patient was unable to stand without assistance Nowhere is there localized atrophy or fibrillation The extensor power of the legs was less than the flexor power There was no tremor present in hands or legs The conjunctival, corneal, palate, and pharyngeal reflexes were normal The biceps, triceps, and supinator reflexes were normal and equal on both sides The abdominal, cremasteric, and external anal reflexes could not be elicited The plantar reflexes were extensor on both sides by Babinski's method, and on the left side by Oppenheim's method The patellar and Achilles tendon reflexes were absent, even on reinforcement There was no ankle or patellar clonus The patient complained of inability to control the movements of the bowels and at times of difficulty in holding the urine Sexual power was absent There was a slight edema of the subcutaneous tissues

Mental Examination—(1) General memory and orientation Memory for past and recent events appeared to be fairly good and the patient related childhood experiences with apparent accuracy The patient said that he entered the hospital September 23, since when he thought he had greatly improved He gave the month as December, which was correct, and the year as 18—then says 1900 Was oriented as to place and persons (2) General understanding and insight appeared to be satisfactory (3) Emotional status He was depressed, as a rule, and had been so for years, however, he had no suicidal tendencies, but said, on the contrary, that he expected to be hopeful to the last minute He complained of having had a good deal of trouble with the devil, who, twenty-five years ago, while the patient was in perfect health, got into the habit of appearing after he had gone to bed at night At these times he would bend over the patient and hold him so firmly at his sides that he would awake from the pain A good deal of prayer finally rid him of this trouble, until the past September when the devil again appeared, tormenting him almost every night for about a month One night, while sleeping in a boarding house, the devil entered and carried on to such an extent that the screaming of both him and the patient caused the neighbors to send in a call for the police He added that, though he was usually asleep when the devil appeared, he was well awake for some time before he left The patient is convinced that God sent these visitations as a punishment for his past iniquity At times he heard the church bells ringing, usually in the left ear, for half an hour at a time Also heard whistling, and words which come from various directions but say nothing (4) Memory Memory for past and recent events appear to be fairly good, though the patient said that of late it had grown poor In repeating the "Cowboy Story," he got to the point at which the cowboy put on his old clothes, but forgot all that followed, omitting the dog from the story altogether and remembering absolutely nothing about it He was able to repeat numbers of four places correctly, but made mistakes in repeating numbers of five or more digits In repeating the alphabet he gave the last letters as q, u, s, t, y, z (5) Attention Attention during the entire examination was found to be satisfactory, the attention tests being performed fairly well (6) Thinking He could do simple calculations, but could not point out the faulty logic in the "Lillies and Roses" test (7) Capability Save for the limitations imposed by his weakness the patient's capability appears to be good There is some slurring in repeating the test phrases (8) Association In the Masselon tests, the patient was unable to build sentences that were to contain three given words Being asked to make a sentence containing the words "kettle," "water" and "stove," he said, "The kettle stood in the water," and in using the words "baby," "bottle" and "milk," he said, "The baby was drinking the bottle" (9) Sleep and dreams The patient sleeps

poorly as he is awakened by the least noise The jerking in his legs also tends to keep him awake

Necropsy—The patient died March 18, 1915, necropsy being performed thirteen hours postmortem The protocol showed the following *External appearances* The body is that of a well developed, fairly well nourished, adult male, 179 cm in length Rigor is present, and there is lividity in the dependent parts The pupils measure 5 mm in diameter and are equal There is a moderate amount of edema in the extremities and in the external genitals There is a small pigmented mole at the angle of the left scapula *Peritoneal cavity* The peritoneal cavity contains about 2,000 c c of clear, straw colored fluid The serous surfaces are smooth and clear and there are no adhesions The appendix measures 9 cm in length and hangs free The diaphragm reaches the fourth interspace on the left and the fourth rib on the right The mesenteric lymph nodes are moderately enlarged and dark in color *Pleural cavities* The left pleural cavity contains 800 c c and the right, 500 c c of a clear, straw colored fluid There are strong fibrous adhesions at the apex and at the posterior portion of the base of the right lung The left pleural cavity is free from adhesions and the serous surfaces are smooth and clear *Pericardial cavity* The pericardial cavity contains about 250 c c of clear, straw colored fluid, the visceral and parietal pericardium being smooth and glistening *Heart* The musculature is thin, soft, flabby, and somewhat pale in color The mural endocardium is smooth and clear and the valve leaflets show no gross lesions The root of the aorta has a few elevated, yellowish patches, but possesses good elasticity, the intima is of a bright red color *Lungs* No nodules are palpable and the lungs crepitate throughout From sections through the posterior portion of the base of the left lung, a large quantity of thin, reddish fluid can be expressed *Spleen* The spleen weighs 200 gm, the capsule is smooth, and the pulp is dark in color and scrapes readily *Liver* The liver weighs 2,850 gm, is of a fairly light, reddish brown color, and on cut section reveals small, dark areas surrounded by lighter zones The pancreas, gastro-intestinal tract, and adrenals show no gross lesions *Kidneys* The kidneys together weigh 360 gm, are equal in size, and slightly lighter in color than normal The capsules strip readily, leaving smooth, glistening surfaces The cortices are of even thickness and the normal markings regular The bladder is normal The bone marrow from the upper third of the femur is yellow in color The anatomic diagnosis was (1) pernicious anemia (aplastic type), (2) ascites, hydrothorax, and hydropericardium, (3) moderate chronic passive congestion of the liver, (4) hypoplasia of the mesenteric lymph nodes, (5) slight atherosclerosis, (6) edema of the left lung, (7) hemoglobin imbibition of the aorta

Sections of the spinal cord stained by the Weigert method show a moderate degree of combined sclerosis of the type seen in pernicious anemia The Marchi sections of the cord are normal in appearance

Brain—The brain is slightly paler than normal The leptomeninges are slightly clouded along the blood vessels of the convexity The vessels at the base are possibly a little thickened The gyri are normal in size and conformation The ventricles are normal in size and the ventricular walls smooth and glistening

Weigert Sections *Sections passing through the brain at the level of the genu corporis callosi* In the marginal gray matter one sees areas of increased pallor at the dividing point of the blood vessels The medullary portion of the section is absolutely normal in appearance Sections through the optic chiasma, 1 cm posterior to the optic chiasma, and the crus, are normal Occipital sections show a slight degeneration of the medullated fibers in the neighborhood of some of the blood vessels In the marginal gray small circular foci, as described in a number of preceding cases, are found in limited numbers Sections through the pons are normal *Sections through the olive and the cerebellum* Just underneath the dentate nucleus of one side appear two small foci of the Lichtheim

type In one of the recessses formed by the folding of the dentate nucleus, the white fibers show definite ballooning and disintegration

Marchi Sections In the right centrum semiovale are seen evidences of recent degeneration, a number of the fibers appearing swollen and in many places represented by rows of blackened globules These changes become progressively more marked in the deeper portions of the brain All of the degeneration seen appears to be recent, none of the blood vessels showing evidences of perivascular accumulations

Bielschowsky Sections In the Bielschowsky sections a number of blood vessels can be seen which are surrounded by a light halo, the fibers within this area showing evidences of disintegration The Weigert glia fiber and the Ramon y Cajal glia cell sections show no evidence of reaction on the part of this tissue Here and there, in the meninges and in certain of the blood vessels there is seen rather extensive invasion of streptococci, but no evidence of reaction In the hematoxylin and eosin sections rather numerous sieve like areas are noted in the medullary substance of the cortex, which vary in size from 0 01 to 0 03 mm, and which, in a number of instances, are found to be definitely related to the blood vessels, though this relation cannot be definitely established in all of them As many as eighteen to twenty of these foci can be counted in the low power field of the microscope One of the meningeal vessels was found to contain a good many leukocytes Thionin, toluidin blue, and neutral red sections show most of the pyramidal cells to be absolutely normal in appearance In a few instances, however, there are found chromatolysis, slight satellitosis, neuronophagia, indistinctness of the cell outline with disappearance of the processes, and some swelling and eccentricity of the nuclei In a good many cells there appears, plastered around the nucleus and the periphery of the cell, a rather deeply staining material which is evidently derived from the Nissl bodies A very few of the cells exhibit a certain degree of vacuolization The changes noted above are found to be most numerous in the Rolandic area The blood vessels at the base show some thickening of the intima and possibly also some of the media, there is a moderate increase in the elastic fibers and some splitting of the inner elastic membrane The *Lichtgruenfuchsin* sections show nothing pathologic

CASE 6—(Necropsy 251) *History*—A T, 37 years of age, Norwegian, died on April 15, 1913, a clinical diagnosis of pernicious anemia having been made by a competent internist Necropsy was performed twenty-three hours postmortem, a standard embalming fluid having been injected the evening before The following notes appear on the record

Necropsy—The body is that of a somewhat emaciated, but well developed adult man There is moderate rigor mortis and slight lividity of the dependent portions Mucous membranes of the throat and mouth are very pale The plural cavities contain about 10 ounces, on the right side, of a clear, yellowish fluid which contains some flakes of fibrin The pericardial cavity is empty and the walls smooth and glistening The abdominal cavity contains no fluid and the viscera, save for pallor, are normal in appearance *Lungs* The right lung weighs 760 gm The lower lobe is heavy and does not collapse The upper lobe, in its dorsal portion, is firm and crepitates feebly, the anterior portion being very pale and normal to the touch On cutting the lower lobe a pale, yellowish red fluid escapes and a number of granular plugs may be scraped out The posterior portion of the upper lobe was filled with a frothy fluid The left lung weighs 650 gm and is very pale and edematous The peribronchial lymph nodes are pigmented and slightly enlarged *Heart* The heart muscle is pale and flabby in consistency The right cavity is filled with a thin, pale bloody fluid The left cavity contains a white coagulum, the walls are fixed to a certain depth by the embalming fluid The valves are normal in appearance The aorta is negative *Spleen* The spleen weighs 300 gm, is somewhat enlarged, pale and firm *Kidneys* The combined weight is 390 gm, the right being a little smaller

than the left The surfaces show the fetal markings The capsule is slightly thickened and strips with a little difficulty, small bits of the cortex being removed with it The cortex is somewhat narrow, the normal markings somewhat indistinct, and the glomeruli rather prominent The left contains a solitary cyst about 1 cm in diameter The ureters, bladder and urethra are negative *Adrenals* These are normal in size, but very pale *Liver* The liver weighs 1,630 gm The capsule is smooth, rather pale and has a rusty tint The gallbladder is filled with a viscid bile and the ducts are patent The pancreas is negative, though very pale *Stomach* The stomach is dilated with a liquid content, the wall is very pale, somewhat thinner than normal, and the mucosa shows no evidence of old ulcers or other irritation The small intestine is pale and contains small amounts of fluid feces, but is otherwise negative The appendix hangs free and is normal in appearance The large intestine contains considerable amounts of feces in masses In places the wall of the intestine is very thin *Retroperitoneal structures* The glands about the aorta and the celiac axis are enlarged and somewhat congested The scalp and the skull are negative *Bones* The clavicle contains marrow which is normal in appearance The ribs and sternum contain a very friable and pultaceous marrow which is a deep reddish chocolate color Smears from the sternum and from the marrow of the fifth rib stained with the Erlich-Biondi stain show erythrocytes, microcytes, polychromatophilia, many megaloblasts, some normoblasts, and white blood cells of all types, including many myelocytes and coarsely granular oxyphils Necropsy diagnosis (1) Anemia of all the viscera, (2) lobar pneumonia of the right lower lobe, with a serofibrinous pleuritis, (3) edema of the left lung and the upper lobe of the right lung, (4) some fatty degeneration of the kidney, (5) slight dilatation of the heart, with possibly some fatty degeneration of the muscle, (6) increase in the red bone marrow, (7) atrophy and dilatation of the stomach, (8) extensive pigment deposit throughout the liver Unfortunately none of the spinal cord was removed at necropsy

Brain—The membranes of the brain are very pale The brain itself is normal in appearance and consistency, save that it is almost pearly white in color The blood vessels at the base of the brain are normal in appearance and very delicate to the touch

Weigert Sections These are all normal save for a few slight changes *Frontal area* In the marginal gray matter and in the medullary substance at various distances from the surface are a number of light circular areas, about 0 1 mm in diameter, which are often seen surrounding capillary vessels cut in cross section *Section through the optic chiasma* Surrounding a number of the smaller capillaries in the medullary substance of the brain there is a small area of disintegration, such as have been described *Sections through the crus* A few circular pale areas, present up to the number of about five to the low power field, and measuring about 0 25 mm in diameter, are seen in some of the medullary rays of the gyri Similar areas are also seen in the marginal gray layer *Occipital lobes* Sections from this area resemble in all respects those just described Sections through the cerebellum are normal in appearance

The Marchi sections show no definite pathologic changes In both the gray and the medullary portions of the cortex, as seen in the Bielschowsky sections, there are noted pale, more or less circular areas, about 0 1 to 0 25 mm in diameter, present in numbers up to four or six to the low power field (No 3 Leitz objective and No 4 eye piece) and resembling in all respects similar areas described in some of the foregoing cases Serial sections show that these, in nearly every instance, are related either to some small blood vessel or surround one of the pyramidal cells of the gray layer The cells themselves, lying within these areas, show no pathologic changes The glia structures in this brain are normal in appearance, with the possible exception of some irregular thickening of the coarser glia fibers Hematoxylin and eosin sections show the same areas of disintegration described in the Bielschowsky sections, the association with the perivascular spaces being well illustrated The cells of the cortex, as stained

with thionin and toluidin blue, are absolutely normal in appearance, with the exception of a small number of cells lying within the degenerated areas, described in the preceding sections These are more readily studied in sections which are somewhat overstained No fuchsinophilic granules are noted The larger blood vessels at the base are normal in appearance

CASE 7—(Necropsy 11-17) *History*—H R, 42 years of age, single and a laborer, was admitted to the hospital Jan 25, 1911, complaining of difficulty in breathing, fatigue on slight exertion, a pain about the heart which was sharp at times, some swelling of the face, and increasing pallor of five weeks' duration The patient was born in Minnesota and had never left the state The father and mother both died of unknown causes His habits were said to have been moderate

Physical Examination—This showed a middle aged man, medium in stature, well developed, and fairly well nourished The hair was brown, with an admixture of gray The eyes were blue, the pupils circular, equal in size, and normal in reaction Hearing was normal The patient stated that he had had some ringing in the ears prior to coming to the hospital, but this had now wholly disappeared The skin was somewhat yellowish in color and extremely pale The mucous membranes were pale and the capillary circulation did not return promptly after pressure The left border of the heart extended to about 1 inch outside of the nipple line There was a blowing sound, systolic in time, heard loudest over the apex, and transmitted over the entire chest The abdomen was negative to palpation, and no masses were felt The muscles were somewhat flabby and there was a moderate loss of strength The spleen was large and palpable The deep reflexes were diminished in the upper extremities and the knee kicks could not be obtained There were no enlarged glands palpable The urine was normal save for an occasional pus cell Examination of the stool showed no ova or parasites Examination of the blood showed the following January 28, hemoglobin 18 per cent, red count 800,000 and 2,500 leukocytes, February 9, hemoglobin 10 per cent, red cells 400,000, 7,000 leukocytes, with an apparent increase in the relative number of lymphocytes, a rather marked poikilocytosis, polychromatophilia, also normoblasts in moderate numbers and megaloblasts in greater numbers The patient exhibited a slight rise in temperature, which fluctuated, but never exceeded 99 6 F The pulse varied between 80 and 100, and the respirations between 20 and 24 The patient was put on dilute hydrochloric acid and nux vomica February 6, there was slight epistaxis He became progressively weaker and on February 10 became very delirious, talking and moving about continually He died February 11

Necropsy—Necropsy was performed five and a half hours after death with the following results *External appearance* The body is that of a fairly well developed, poorly nourished, adult male, 168 cm in length The skin is very pale and mottled on the arms and neck by freckle patches Rigor mortis and lividity are absent The pupils measure 6 mm and are equal There is no edema, cyanosis or jaundice *Peritoneal cavity* The surfaces are everywhere pale but smooth and glistening The right lobe of the liver in the midclavicular line reaches 3 cm below the costal margin The left lobe of the liver is very prominent, reaching 11 cm below the xyphoid cartilage The appendix is 7 cm in length and is bound by adhesions to the root of the mesentery, on the left side at its tip Near the tip the lumen of the appendix is obliterated The mesenteric lymph nodes are normal The diaphragm reaches to the fifth space on the left, and to the fifth rib on the right *The pleural cavity* The pleural cavities are interrupted by numerous stretched fibrous bands There is no free fluid in the cavity The pericardial cavity is normal, except for a large grayish white patch on the anterior surface of the right ventricle *Heart* The heart weighs 418 gm The muscle is very pale but of firm consistance The cavities are filled with clots and are all somewhat dilated These clots are composed of definite layers, the upper portions having the appearance of "goosefat," while

the lower layers are much paler than normal The valve leaflets are apparently normal The root of the aorta shows an occasional raised grayish patch of thickening The tricuspid valve measures 15 mm, the pulmonary valve 8 mm, the mitral valve, 9 5 mm, the aortic valve 8 mm The depth of the right ventricle is 10 cm, and the thickness 0 6 cm The depth of the left ventricle is 9 5 cm and the thickness, 1 4 cm *Lungs* The lungs are quite pale and remarkably free from black pigment There is no evidence of postmortem congestion of the dependent portions The lung pulp is free from nodules or tubercles In the peribronchial lymph nodes of the left lung there is one small calcareous nodule A similar nodule exists in the lymph node at the bifurcation of the trachea *Spleen* The spleen is small and regular, weighing 85 gm The pulp is increased in consistence, of normal color, and on cut surface, aside from comparative obscurity of the malpighian bodies, appears normal *Liver* The liver weighs 1,695 gm The surface and pulp are pale and very moist, the pulp having a swollen feeling The gallbladder is distended with thin bile and the ducts are normal *Gastro-intestinal tract* The mucous membrane throughout is very pale The pylorus shows apparent definite thickening, but there is no evidence of any lesion throughout the tract Peyer's patches, in the lower portion of the ileum, are raised, prominent, and slightly roughened on their surfaces *Adrenals* The adrenals are free from demonstrable lesion *Kidneys* The kidneys weigh 310 gm The capsules strip readily, leaving smooth surfaces The pulp of the left kidney is very pale and the markings are indistinct In the pulp of the right kidney, there is a slight yellowish tinge in the cortical portion, and the striae are fairly regular The bladder is distended with a clear urine *Genital organs* The prostate shows occasional dark pigmented points The aorta contains numerous raised, grayish white or grayish yellow nodules *Organs of the neck* The thyroid and trachea are normal *Head* The scalp, calvarium, and dura are normal The base of the skull and the middle ears are normal in appearance *Bone marrow* The bone marrow of the right femur throughout its entire extent is very red, soft, and of a thick, oily consistence The bone marrow of the ribs is very red and prominent The necropsy diagnosis is (1) primary anemia of an acute type, (2) old healed tuberculous pleuritis, (3) edema of the brain, (4) chronic obliterating appendicitis, (5) possible thickening of the pyloric ring Bacterial examination A culture from the heart's blood is negative Microscopical examination The muscle fibers of the heart are in good condition There is almost complete absence of blood from the capillaries There is a patch of scar tissue under the pleura and some emphysema The spleen is normal The liver shows no blood in the sinuses The hepatic cells show an increase of pigment and large numbers of fat droplets The stomach is normal except for a little postmortem change, which is also true of the intestinal tract The adrenals are normal The convoluted tubules of the kidney are somewhat dilated, the epithelial cells are in good condition, and there is no increase in connective tissue The aorta shows a slight thickening of the intima The thyroid gland is normal The sinuses of the lymph nodes are very prominent and contain large numbers of leukocytes, many of the polymorphonuclear type The prostate is normal The testicles contain no spermatazoa, but are otherwise normal The pituitary gland is apparently normal The bone marrow shows the typical structure of red bone marrow, there are large numbers of myelocytes, nucleated reds, etc, but very little adipose tissue cells

Brain—The brain weighs 1,305 gm There is no distinct evidence of lesion except for a marked edema of the pia arachnoid and some pallor The blood vessels are empty and slightly thickened at the base The ventricles and gyri are normal The spinal cord, of which sections could be obtained only from the extreme upper end, appears to be normal

Weigert Sections *Frontal area* In the medullary portions of the frontal area are seen three blood vessels, surrounding which there is an evident destruction of the medullated fibers *Sections through the optic chiasma* Two

plaques about 0 2 by 0 4 mm in size are seen, one in the corpus callosum, and the other in the white matter just under the marginal gray These resembled in all respects the Lichtheim foci of the cord *Sections through the crus and through the occipital lobes* Aside from two or three small areas of destruction, these sections appear to be normal *Sections through the cerebellum and through the pons* are normal The Marchi sections of the cortex show a very slight stippling, which is probably pseudo-Marchi in character A few ballooned myelin sheaths are found There are no accumulations about the blood vessels

Bielschowsky Sections In the Bielschowsky sections a very limited number of lighter plaques, similar to those described in preceding cases were seen, both in the white and in the marginal gray In this case, however, the association of these plaques with blood vessels or pyramidal cells was less constant In all of the sections stained by the Ramon y Cajal stain and by the Weigert glia fiber method there appears to be some increase in the size of the glia cells, as well as some enlargement, and possibly some proliferation of the glia fibers The hematoxylin and eosin sections show nothing abnormal save a marked satellitosis Sections stained with thionin, toluidin blue, and neutral red show a well marked satellitosis, occasional tigrolysis, and eccentricity of the nuclei In sections which are somewhat overstained one can see a number of the pale areas, both in the marginal gray and in the medullary portions, which are most numerous in the temporal lobes, where one or two can be seen in from one to six low power fields Some of the pyramidal cells within these areas appear somewhat shrunken and rather deeply stained, others show a marked tigrolysis and vacuolization, with indistinctness of the cell membrane The basal nuclei appear normal No fuchsinophilic granules are seen in any of the sections The larger blood vessels from the base show a slight, diffuse arteriosclerosis, which involves principally the media, also a slight and diffuse increase in the amount of elastic tissue

DISCUSSION

Certainly it cannot be said that the cortex of pernicious anemia patients is barren of pathologic findings The lesion of prime interest is, of course, the occurrence of placques in the medullary substance of the cortex, which in every respect resemble the lesions so often found in the spinal cord While the cases reported by Barrett all had a very marked mental disturbance associated with the pernicious anemia, this obtains in only one case of this series, the mental condition of the patient in the remainder being no more altered than is usually seen in pernicious anemia In three of the seven brains studied, this focal degeneration could readily be seen with the naked eye, in two it was of moderate intensity, requiring a microscope for its detection, and in two it was very slight, indeed, only a very few small areas having been noted

The incongruity between cases presenting cord symptoms clinically and those showing pathologic changes at subsequent examination has long been a matter of comment, thus, also, in Case 4 there was marked clinical evidence of cord involvement, while pathologically there appeared only a very slight degeneration as shown in the Weigert sections, though in the Marchi sections this change was more evident On the other hand, in the same case the mental symptoms were very slight and no change in the mentality appeared until just preceding death,

while the degenerative changes in the brain were very marked If one considers only those cases in which there existed a definite psychosis, this lack of correlation between the clinical and pathologic findings is even more striking Although Barrett found definite pathologic changes in ten of the eleven cases which he reports, the Lichtheim placques were present in only four, and very insignificant in the mental case here reported, on the other hand, in four of the seven cases of this series, the degeneration was very marked, while the mental symptoms were no more marked than is ordinarily observed in pernicious anemia Just what part these lesions play in the production of this mental condition cannot be definitely stated As Barrett and others have shown, the development of well marked psychotic manifestations is probably independent of the pernicious anemia itself The same lack of causal relationship between the mental symptomatology and the pathologic changes observed, probably obtains with reference to these placques also It is not at all unlikely, however, that they may aid in the production of the indifference, irritability, apathy, and somnolence so frequently seen, though the principal factor underlying these phenomena is probably the toxin itself

The percentage of pernicious anemia cases showing pathologic lesions in the cord is rather high, though an accurate figure cannot be given Nonne, in a series of seventeen cases, found cord changes present in ten, about 59 per cent Minnich, in thirty cases, found changes in twenty-three, about 77 per cent, Petrén, in nine cases, found changes in two, about 22 per cent In the five cases of this series in which the spinal cord could be studied, combined sclerosis was marked in three, moderate in one, and very slight in one

Compared to this it will be seen that the degenerative changes in the medullary portion of the cortex occur fully as often in pernicious anemia, if not oftener, than do changes in the spinal cord, though the lesions in the brain are usually smaller, fewer in number, more widely scattered and not so readily enlarged by confluence and secondary degeneration, which renders their detection more difficult In Cases 1, 2, and 3 there was a well marked change in both the brain and the spinal cord, in Case 4 the changes in the brain were marked while those in the spinal cord were relatively slight, in Case 5 the degeneration of the brain was very slight while that in the cord was moderate If the results of such a small series of cases can be used in formulating a general principle, it might be said that the changes in the cord and in the brain run fairly parallel

Of not less importance, however, are the smaller areas which were described in the Weigert sections as being more or less circular in outline, about 0 1 mm in diameter, and most numerous in the medullary

portion of the cortex, just underlying the marginal gray of the convolutions The same areas appeared in other slides as localized patches in which the fibrillar structure was more or less pushed aside, the meshes being thereby enlarged, the margins were not well defined, but graded almost insensibly into the surrounding tissue, the entire structure presenting a picture such as might be brought about by a localized edema As serial sections showed, they may be unrelated to any blood vessels, though as a rule they tend to surround these like a halo Axis cylinders passing through these areas were found to be more or less disintegrated, and in the center of a number of them was seen an accumulation of granular debris, as shown in Figure 13 There was no evidence of any associated glia reaction or cellular increase In a number of instances these meshes were found to be more or less distended with a somewhat hyaline, usually basophilic substance, which resembled in every respect material found in the perivascular spaces, and with which it at times seemed to be continuous, as though it had been pressed into the tissues Such a condition is represented in Figures 14 and 15 There appears to be but one conclusion, and this is the obvious one, which is that at least some of the white fibers, including the myeline sheaths and the axis cylinders, are destroyed, presumably through toxic action, possibly assisted by stasis, by a substance which accumulates in the so-called perivascular space The very marked degeneration seen around some of the vessels in the Marchi sections, as well as the Weigert sections, supports this theory as additional evidence It was also noted, however, that these perivascular structures were not the only ones in which this degeneration was initiated, but that a very diffuse and widely scattered destruction of the medullary substance at times occurred To state that this is due directly to toxin action is rather arbitrary, though it certainly appears by virtue of its apparent simplicity to be the case, and it is not only possible, but also probable, that such a mechanism may obtain

There is another factor, however, which the study of this material shows to be instrumental also in bringing about degeneration in the medullary substance of the cortex It will be recalled that in Cases 2, 3, 6, and 7 certain areas of pallor, resembling very closely those just referred to, were also present in the marginal gray matter of the gyri These were, in perhaps the majority of instances, found surrounding a pyramidal cell, as shown in Figures 16, 17, 18 and 19, the cell thus located presenting all degrees of degeneration from one which was practically normal in appearance to one which was completely disintegrated, the cells in the vicinity being practically normal as revealed by microscope It seems indisputable that this cellular disintegration and the surrounding area of partial necrosis bear some relation to one

another The interpretation of this, however, is not so simple We are probably justified in assuming that the process at work here does not differ materially from that acting to bring about degeneration in other structures of pernicious anemia brains Accordingly, this cellular destruction is probably the result of some toxin action, assisted possibly by some nutritive factors of mechanical origin The manner in which this toxin is conveyed to the cell is probably the same as elsewhere, namely, through the lymphatic channels, incidentally this would serve as additional evidence of the existence of a so-called pericellular space of Obersteiner Granting that pyramidal cells of the cortex may be thus destroyed, there would then follow a secondary degeneration of the axon to which it gives rise, which would account for at least some of the degenerating fibers seen in the cortical white matter

Certain other cell changes were observed also, though, on the whole, the cells were practically normal in appearance Among the changes seen, were varying degrees of tigrolysis, particularly in the cells of the second and third pyramidal layers, vacuolization, loss of cell processes, indistinctness of the cell outline, eccentric positions of the nuclei and of the nucleoli, some of which were very much swollen, deep staining of the nucleus, partial extrusion of the nucleus, and in two cases, definite axonal reaction Satellitosis and neuronophagia were observed also Fuchsinophilic granules were seen in the cells of a number of cases In certain cells there appeared to be an increase in the amount of intracellular pigment which exceeded the normal, on the whole, however, this was not the case

Relative to the glia changes, little can be said There appeared to be in some of the cases a little increase in the coarser glia fibers, which often seemed enlarged, nodular, and very wavy Henneberg's observation, that there is in general little glia reaction in cases of this kind, due possibly to the poor nutritional state, would seem to be borne out by these findings Too much can hardly be said in praise of Ramon y Cajal's comparatively new gold stain for glia cells and the coarser glia fibers We found it to yield very excellent pictures

Hemorrhages were noted in but one case, and here they were not very numerous Definite softening was observed in two of the cases, once involving a portion of the basal nuclei, and in another, the cortical white matter The "Ringwallherdchen" described by Schroeder as being so characteristic of pernicious anemia brains, though carefully sought, could not be found, though it seems that this should be no difficult task, in view of his description Only one focus, in which the resemblance was, as a matter of fact, exceedingly remote, was found which could possibly be interpreted as an accumulation of disintegrated glia cell neuclei

SUMMARY

Summarizing again what we believe to be the most salient features in the pathologic anatomy of pernicious anemia brains, we have the following

1 Not only do degenerated areas of the Lichtheim type, such as are typically found in the posterior and lateral funiculi of the spinal cord in pernicious anemia patients, occur in the medullary portions of the brains of these cases, but they occur with about the same frequency, though their demonstration may be rendered more difficult

2 Patients who show degenerative changes in the spinal cord at necropsy, usually show the same type of lesion in the brain also

3 In addition to these focal degenerative areas found in the white matter, which may or may not be associated with blood vessels, we also find a diffuse degeneration, which, though it is, as a rule, somewhat more striking in the long association tracts, also occurs in the short commissural fibers passing from one gyrus to another, thus rendering the view untenable that it is the distance of these fibers from their trophic centers which is instrumental in causing the degeneration

4 The gray matter is by no means immune from the destructive process This is usually focal in character, and begins around the pyramidal cells of the marginal gray layer, the cells themselves being ultimately destroyed in the process, this, in turn, giving rise to a secondary and very diffuse degeneration of the medullated fibers in the white matter

5 Though some degeneration was noted in the fibers of the internal capsule and in the long tracts passing through the pons, the degeneration at this level was less intense than that seen either in the cord or in the brain

6 The appearance of these plaques, not only around the blood vessels but also around some of the larger pyramidal cells, seems additional evidence that lymph stasis is an important factor in the production of these foci

7 Well marked psychoses, such as are occasionally associated with pernicious anemia, probably have little or nothing to do with these destroyed areas

8 The milder mental manifestations such as somnolence, apathy, and terminal delirium, are probably in a measure dependent on these lesions, though the chief causative agent of these symptoms is probably the toxin itself

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BOOK REVIEW

THE ELEMENTS OF THE SCIENCE OF NUTRITION By Graham Lusk, Ph D , Sc D , F R S (Edin), Professor of Physiology at Cornell Medical School, New York Third Edition W B Saunders Company, 1917

This book in its first two editions has been so well known among physicians and scientists that it seems almost superfluous to describe it Professor Lusk reviews the evidence on which the science of nutrition both in normal and pathologic states is based, he furnishes us with a critical analysis of the intricate subject which we as clinicians have tersely designated as "metabolism in health and disease" It requires a man who is not only a master in this subject, but in his power of expression as well, to present this material in an acceptable form The author of this book fulfils both of these requirements in a wonderful manner He has succeeded in describing the experimental evidence in each instance very briefly, and yet in such a way, usually by the judicious use of tables and figures, that the proof of each contention is vivid and very positive The reader under these circumstances is able to form a concrete idea of the actual work accomplished by each author referred to in the text and to follow step by step in a most logical way the evidence which leads to Professor Lusk's conclusions The discussions concerning calorimetry, the influence of protein, fat and carbohydrate, and of normal diet under various conditions are elaborated in great detail Diseases such as diabetes and gout, which fall in the category of metabolic disorders, are carefully discussed from the scientific and experimental point of view The third edition is much larger than previous ones, and includes a consideration of all of the most recent literature To physiologists, physiologic chemists and physicians interested in nutrition or nutritional diseases this book is indispensable

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